EU Risk Management Plan

for

Privigen®
(Human Normal Immunoglobulin for Intravenous Administration)

RMP version to be assessed as part of this application:

RMP Version number:	9.1
Data lock point for this RMP:	31 December 2025
Date of final sign off:	12 February 2026
Rationale for submitting an updated RMP:	Further updates requested by EMA for Submission of a Variation: Addition of the indication for measles pre- / post-exposure prophylaxis for susceptible persons in whom active immunisation is contraindicated or not advised
Summary of significant changes in this RMP:	Addition of measles pre- / post exposure prophylaxis as an indication in alignment with the EMA Core SmPC for IVIG 2021
Details of the currently approved RMP:	
RMP Version number:	8.0
Approved with procedure:	EMEA/H/C/000831/II/0161/G
Date of approval (opinion date):	20 January 2020
QPPV name:	Dr. med. Juergen Zorn
QPPV signature:	e-signature (see last page)

Abbreviations

Term / Abbreviation	Description
AIDS	Acquired immunodeficiency syndrome
ATC code	Anatomic Therapeutic Chemical code
CI	Confidence interval
CIDP	Chronic inflammatory demyelinating polyneuropathy
CLL	Chronic lymphocytic leukemia
CSLB	CSL Behring
EU	European Union
EEA	European Economic Area
GBS	Guillain-Barré syndrome
HCT	Haematopoietic stem cell transplantation
HIV	Human immunodeficiency virus
IgG/A	Immunoglobulin G / A
IV	Intravenous
IVIg	human normal immunoglobulin 10% solution for intravenous administration
ITP	Primary immune thrombocytopenia
MM	Multiple myeloma
MMN	Multifocal motor neuropathy
PID	Primary immunodeficiency
PSAF	Proven specific antibody failure
RMP	Risk Management Plan
SID	Secondary immunodeficiency
SmPC	Summary of Product Characteristics
USA	United States of America
WHO	World Health Organization

Table of Contents

List of Tables

Part I: Product(s) overview

Table Part I-1: Product(s) overview

Active substance(s) (INN or common name)	Human normal immunoglobulin 10% solution for intravenous administration (IVIg)
Pharmacotherapeutic group(s) (ATC Code)	Group: Immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration ATC Code: J06BA02
Name of Marketing Authorisation Holder	CSL Behring
Medicinal products to which this RMP refers	Privigen®
Invented name(s)	Privigen (Human Normal Immunoglobulin for Intravenous administration)
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Privigen belongs to the pharmacotherapeutic group of immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration.
	Summary of mode of action: The active substance in Privigen is human normal immunoglobulin, mainly (> 98%) immunoglobulin G (IgG). IgG has a wide range of activities against organisms that can cause infection. Privigen restores abnormally low IgG plasma levels to their normal range. At higher doses, Privigen can help to adjust an abnormal immune system and modulate the immune response.
	Important information about its composition: Privigen is prepared from pooled human plasma by a combination of cold ethanol fractionation, octanoic acid fractionation, and anion exchange chromatography. CCI [redacted]

CCI [redacted]

	CCI [redacted]
Hyperlink to the Product Information	Privigen SmPC
Indication(s)	Current: *Replacement therapy in adults, and children and adolescents (0 to 18 years) in:* • Primary immunodeficiency (PID) syndromes with impaired antibody production • Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)[a] or serum level of < 4 g/l. [a] PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines. *Immunomodulation in adults, and children and adolescents (0 to 18 years) in:* • Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count • Guillain-Barré syndrome (GBS) • Kawasaki disease • Chronic inflammatory demyelinating polyneuropathy (CIDP) • Multifocal motor neuropathy (MMN)
	Proposed: *Replacement therapy in adults, and children and adolescents (0 to 18 years) in:* • Primary immunodeficiency (PID) syndromes with impaired antibody production • Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)[a] or serum level of < 4 g/l.

[a] PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines.

Measles pre- / post-exposure prophylaxis for susceptible adults, children and adolescents (0 to 18 years) in whom active immunisation is contraindicated or not advised.

Consideration should also be given to official recommendations on intravenous human immunoglobulin use in measles pre- / post-exposure prophylaxis and active immunisation.

Immunomodulation in adults, and children and adolescents (0 to 18 years) in:

- Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count
- Guillain-Barré syndrome (GBS).
- Kawasaki disease
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)

Dosage

Current:

Indication	**Dose**	**Frequency of infusions**
Replacement therapy		
Primary immunodeficiencies (PID)	starting dose: 0.4-0.8 g/kg body weight (bw) maintenance: 0.2-0.8 g/kg bw	every 3-4 weeks to obtain IgG trough levels of at least 6 g/l
Secondary immunodeficiencies	0.2-0.4 g/kg bw	every 3-4 weeks to obtain IgG trough levels of at least 6 g/l
Immunomodulation		
ITP	0.8-1 g/kg bw or 0.4 g/kg bw/d	on day 1, possibly repeated once within 3 days for 2-5 days
GBS	0.4 g/kg bw/d	for 5 days
Kawasaki disease	1.6–2 g/kg bw	in divided doses over 2-5 days in

	or 2 g/kg bw	association with acetylsalicylic acid in 1 dose in association with acetylsalicylic acid
CIDP	starting dose: 2 g/kg bw maintenance dose: 1 g/kg bw	in divided doses over 2-5 days every 3 weeks over 1-2 days
MMN	starting dose : 2 g/kg bw maintenance dose: 1 g/kg bw or 2 g/kg bw	over 2 to 5 consecutive days every 2 to 4 weeks or every 4 to 8 weeks over 2 to 5 days

Proposed:

Indication	**Dose**	**Frequency of infusions**
Replacement therapy		
Primary immunodeficiencies (PID)	starting dose: 0.4-0.8 g/kg body weight (bw) maintenance: 0.2-0.8 g/kg bw	every 3-4 weeks to obtain IgG trough levels of at least 6 g/l
Secondary immunodeficiencies	0.2-0.4 g/kg bw	every 3-4 weeks to obtain IgG trough levels of at least 6 g/l
Measles pre- / post-exposure prophylaxis		
Post-exposure prophylaxis in susceptible patients	0.4 g/kg bw	As soon as possible and within 6 days, possibly to be repeated once after 2 weeks to maintain the measles antibody serum level > 240 mIU/ml
Post-exposure prophylaxis in PID / SID patients	0.4 g/kg bw	In addition to maintenance therapy, given as an extra dose within 6 days of exposure

	Pre-exposure prophylaxis in PID / SID patients	0.53 g/kg bw	If a patient receives a maintenance dose of less than 0.53 g/kg bw every 3 to 4 weeks, this dose should be increased once to at least 0.53 g/kg bw.
	Immunomodulation		
	ITP	0.8-1 g/kg bw or 0.4 g/kg bw/d	on Day 1, possibly repeated once within 3 days for 2-5 days
	GBS	0.4 g/kg bw/d	for 5 days
	Kawasaki disease	1.6–2 g/kg bw or 2 g/kg bw	in divided doses over 2-5 days in association with acetylsalicylic acid in 1 dose in association with acetylsalicylic acid
	CIDP	starting dose: 2 g/kg bw maintenance dose: 1 g/kg bw	in divided doses over 2-5 days every 3 weeks over 1-2 days
	MMN	starting dose : 2 g/kg bw maintenance dose: 1 g/kg bw or 2 g/kg bw	over 2 to 5 consecutive days every 2 to 4 weeks or every 4 to 8 weeks over 2 to 5 days
Pharmaceutical form(s) and strengths	Current: *Pharmaceutical form:* Solution for infusion. *Strength:* Privigen is a 10% solution containing 100 mg/mL of total human plasma protein with a purity of at least 98% IgG.		

	Proposed: Not applicable
Is the product be subject to additional monitoring in the EU?	No

EU = European Union; INN = International Nonproprietary Name; RMP = risk management plan

Part II: Safety Specification

Part II: Module SI - Epidemiology of the indication(s) and target population

Indications

Replacement therapy in adults, and children and adolescents (0 to 18 years) in:

- Primary immunodeficiencies (PID) syndromes with impaired antibody production.
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum level of < 4 g/l.

*PSAF = failure to mount at least a 2-fold rise in immunoglobulin G (IgG) antibody titer to pneumococcal polysaccharide and polypeptide antigen vaccines.

Measles pre- / post-exposure prophylaxis for susceptible adults, children and adolescents (0 to 18 years) in whom active immunisation is contraindicated or not advised.

Consideration should also be given to official recommendations on intravenous (IV) human immunoglobulin use in measles pre- / post-exposure prophylaxis and active immunisation.

Immunomodulation in adults, and children and adolescents (0-18 years) in:

- Primary immune thrombocytopenia (ITP) in patients at high risk of bleeding or prior to surgery to correct the platelet count
- Guillain-Barré syndrome (GBS)
- Kawasaki disease
- chronic inflammatory demyelinating polyneuropathy (CIDP)
- Multifocal motor neuropathy (MMN)

PID syndromes with impaired antibody production

Incidence:

Estimates of PID incidence are limited. A rate of 10.3 per 100,000 person years was ascertained via a prospective cohort study within a single county in the US from 2001 to 2006 (Joshi et al, 2009). Utilising this rate, PID incidence has been estimated as 718,326 worldwide, 76,148 in Europe, and 35,799 in North America in 2011 (Bousfiha et al, 2013).

Prevalence:

Worldwide prevalence of PID has been estimated to range from 390, 546 to nearly 7 million persons depending on the data source utilised (Bousfiha et al, 2013). A study using claims data provided a 2007 prevalence estimate of PID in the United States of 50.5 per 100,000 privately insured persons and 41.1 per 100,000 publicly insured persons (Kobrynski et al, 2014). This estimate may be subject to overestimation given the limited ability to validate claims however the population covered in this recent study is much larger and demographically diverse than previous studies which estimated prevalence using household surveys at 1 in 1200 for persons of all ages and 1 in 2000 for children (Boyle and Buckley, 2007). The estimated prevalence of diagnosed PID in Europe is between 41,000 and 638,000 (Bousfiha et al, 2013).

Demographics of the population in the authorised indication and risk factors for the disease:

Demographics: Estimated incidence of PID is greater in children 0 to 4 years of age as compared to older children and adults (Bousfiha et al, 2013). Among the paediatric population males are affected more frequently by PID than females although in the population overall, females are affected more (Kobrynski et al, 2014). Data on race and ethnicity is limited though 1 report using US public insurance data found that Nonhispanic Caucasians had prevalence nearly 2 times higher than African Americans and Hispanics (Kobrynski et al, 2014).

Risk factors for the disease: PID is caused by hereditary factors alone. As such the only known risk factor for the development of PID is familial consanguinity (Cooper et al, 2003).

The main existing treatment options:

Main treatment options for PID include replacement of gammaglobulins, aggressive use of antibiotics, and chronic prophylactic treatment with antibiotics (Cooper et al, 2003). Referral to a center with expertise in immunodeficiency should be part of patient management (Cooper et al, 2003).

Natural history of the indicated condition in the population, including mortality and morbidity:

In a retrospective epidemiology study over a 31-year period, the proportion of patients surviving 10 years after diagnosis of PID was 93.5%, although older age at diagnosis was associated with higher mortality (Joshi et al, 2009). A more recent analysis of paediatric patients hospitalised with PID in the United States determined overall mortality of 1.99% that remained consistent over a 9 year follow-up period (Rubin et al, 2018).

Common PIDs include disorders of humoral immunity (affecting B-cell differentiation or antibody production), T-cell defects and combined B- and T-cell defects, phagocytic disorders, and complement deficiencies. Major features of these disorders include multiple infections despite aggressive treatment, infections with unusual or opportunistic organisms, failure to thrive or poor growth, and a positive family history (Cooper et al, 2003; Notarangelo et al, 2004).

Irrespective of the cause, antibody deficiencies result in increased susceptibility to infection with encapsulated bacteria, particularly *S. pneumoniae* and *H. influenzae*. Patients with antibody deficiencies develop recurrent and / or persistent infections typical of these organisms such as pneumonia, otitis, and sinusitis. More severe and invasive infections caused by these organisms (eg, sepsis, meningitis, epiglottitis, cellulitis, empyema and septic arthritis) are also common along with sequelae such as chronic lung disease (Cooper et al, 2003; Kobrynski et al, 2014).

Important comorbidities:

PID disorders are lifelong conditions and the clinical course, even for the same PID type, varies from individual to individual depending upon degree of immunodeficiency, age at diagnosis and level of ongoing management. There are more than 150 types of immunodeficiency described and categorised. Some of these are part of a wider syndrome in the patient, which will include comorbidities in various organ systems, and some are

characterised purely by the immunodeficiency. Co-morbidities are thus varied between patients.

The common element to immunodeficiencies is the increased susceptibility to infection. Often these infections are mucosal in location and become chronic, leading to mucosal damage and comorbidity associated with this damage, for example, bronchial infections leading to bronchiectasis. These comorbidities are consequences of the underlying condition and prevention of these is the aim of therapy. Thus, the later the diagnosis, the more likely some comorbidity will exist.

Considering the spectrum of the various disorders and their general rarity, there are no common comorbidities that may represent a potential risk with the use of Privigen in PID patients.

SID in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either PSAF* or serum level of < 4 g/l.

* PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines.

Examples of SID:

Hypogammaglobulinemia and recurrent bacterial infections in patients with chronic lymphocytic leukemia (CLL) and multiple myeloma (MM)

Incidence:

CLL is the most common form of leukemia in Western countries. Global age-standardised incidence has been estimated at 191 (95% confidence interval [CI]: 179 to 204) per 100,000 person-years (Fitzmaurice et al, 2017).

The age-adjusted incidence rate of MM worldwide is approximately 154 (145 to 162) per 100,000 person-years (Fitzmaurice et al, 2017).

Prevalence:

Worldwide prevalence of CLL has been estimated at 906 (95% CI: 856 to 956) per 1000 persons in 2017 (GBD, 2017 Collaborators).

Up to 85% of patients with CLL have hypogammaglobulinemia which worsens as the disease progresses (Hamblin and Hamblin, 2008; Morrison, 2010). Infections are thought to cause up to 50% of all deaths of patients with CLL (Hamblin, 1987; Oscier et al, 2012).

Prevalence of MM worldwide has been estimated at 449 (95% CI: 415-521) per 1000 persons (GBD 2017 Collaborators). Individuals with MM who suffer from hypogammaglobulinemia (Saba et al, 1979) are at increased risk of infection.

Demographics of the population in the authorised indication and risk factors for the disease:

Demographics: CLL and MM are both considered to be diseases of advanced age. Males consistently have a higher prevalence and incidence of CLL and MM (Fitzmaurice et al, 2017; GBD 2017 Collaborators). Median age at diagnosis of MM is 69.9 years (Kristinsson et al, 2007).

Risk factors for the disease:

CLL: Risk factors for the onset of CLL include the following (Ghia et al, 2007):

- Gender: CLL is more common in males than females, with a ratio of 1.5 to 2:1.
- Age: the incidence of CLL increases with age.
- Genetic and familial predisposition: the risk of developing CLL is 2 to 7 times higher in first relatives of CLL patients compared to the general population.

MM: Risk factors for MM include the following:

- Age: MM has a high incidence rate in the elderly (Katagiri et al, 2013). One-third of MM patients are 75 years old or older at diagnosis (Castelli et al, 2013).
- Genetics: genetic background plays a role in MM susceptibility (Martino et al, 2014).

The main existing treatment options:

CLL: Main treatment options for CLL include:

- Purine analogues are the gold standard for first-line treatment in CLL. Among others (eg, cladribine, pentostatin) fludarabine is the most extensively studied in the western world and it is now the most used (Ghia et al, 2007).

- At present, alkylator-based therapies (such as chlorambucil) are only indicated when palliation of symptoms is the goal of treatment (Ghia et al, 2007).

MM: MM remains an incurable disease in most cases due to frequent relapses (Castelli et al, 2013), with the main treatment options summarised as follows:

- High-dose chemotherapy with autologous stem-cell transplantation is the standard strategy for newly diagnosed young MM patients (Katagiri et al, 2013).
- Drug therapy: immunomodulatory drugs (thalidomide, lenalidomide, pomalidomide) and proteasome inhibitors (bortezomib, carfilzomib) have improved outcomes and extended survival in patients with relapsed and / or refractory MM (Castelli et al, 2013). Combined therapy can be used to prevent or overcome treatment resistance, and increase the efficacy of standard treatment regimens (Castelli et al, 2013).

Natural history of the indicated condition in the population, including mortality and morbidity:

CLL: Irrespective of the initial presentation, the natural course of CLL is very heterogeneous; survival ranges from months to decades with a median of about 7.5 years. Most patients will eventually die with their disease rather than from it and though great progress has been made in therapeutically controlling the symptoms due to the disease, a complete cure is still an extremely rare event (Ghia et al, 2007). Between 1973 and 2013, 11,179 patients with CLL were recorded in a Swedish cancer registry. In all age groups, 5-year and 10-year relative survival ratios (defined as the observed survival in the patient group divided by the expected survival of a comparable group from the general population) significantly improved ($p < 0.0001$) from 0.46 and 0.24 respectively in 1973 to 1979 to 0.73 and 0.53 respectively in 1994 to 2003 (Kristinsson et al, 2007).

MM: The prognosis for MM is severe, with a median survival after diagnosis of approximately 3 years. MM accounts for 1.5 to 2% of all cancer deaths (Castelli et al, 2013). MM is clinically characterised by destructive bone lesions, anemia, hypercalcemia and renal insufficiency (Castelli et al, 2013). Patients with symptomatic disease have an increased risk of infection; however, this decreases with response to therapy (Palumbo and Cerrato, 2013) MM accounts for 10% of all hematologic malignancies in the elderly (Katagiri et al, 2013). In a Swedish cancer registry, relative survival ratio was calculated for 21,502 patients with MM.

One-year survival in all age groups significantly improved ($p < 0.001$) from 0.69 in 1973 to 1982 to 0.82 in 2003 to 2013. Improved 5 and 10-year survival was confined to patients less than 70 years of age (Thorsteinsdottir et al, 2018).

Important comorbidities:

There is a paucity of information about the spectrum or frequency of comorbidities in patients with CLL. Diseases that have been reported infrequently in association with CLL include hematologic neoplasms (eg, Hodgkin's disease, polycythemia vera, myelodysplastic syndrome), disorders with an autoimmune basis (eg, Sjogren's syndrome, rheumatoid arthritis, systemic lupus erythematosis, pernicious anemia), and other disorders such as ITP, Kaposi's sarcoma, nephritic syndrome, bullous pemphigoid, vasculitis and hepatorenal syndrome (Cines et al, 2002; Rozman et al, 1995). It is not considered that these comorbid diseases would represent a potential risk with the use of Privigen in patients with CLL.

Other than common diseases of advanced age, no other comorbid diseases associated with myeloma were identified from the literature (Badros et al, 2001; Coebergh et al, 1999).

There is a known association between treatment with intravenous immunoglobulin (IVIg) and thromboembolic events, particularly in patients of advanced age and with underlying risk factors including immobility and vascular disease. Given the demographic profile of the patient population, there may be potential risk of thromboembolic events in patients with CLL; however, the benefit of treatment should be weighed against the potentials risks, which are considered to be similar to that of other IVIg products.

Hypogammaglobulinemia in patients after allogeneic haematopoietic stem cell transplantation (HCT)

In 2016, 17,641 allogeneic transplantation procedures were performed in 49 European and affiliated countries as a result of leukemia, lymphoma, solid tumors and nonmalignant disorders (Passweg et al, 2018). In the United States, the most comprehensive estimate of allogeneic HCTs is 8539 (D'Souza et al, 2017).

Demographics of the population in the authorised indication and risk factors for the disease:

Demographics: The use of allogeneic HCT varies significantly between countries and continental regions. In a study of paediatric patients following allogeneic HCT

hypogammaglobulinemia (IgG < 500 mg/dL) developed in 77% (n = 143) of the patients at a median of 56 days post-transplantation (Frangoul et al, 2013).

Risk factors for the disease: A higher risk of hypogammaglobulinemia post HCT is associated with low pre-transplant IgG levels, younger age, diagnosis of malignant disease, and the development of acute graft-versus-host-disease (Frangoul et al, 2013).

The main existing treatment options:

Main treatment options for hypogammaglobulinemia post-HCT include:

- IVIg replacement, which restores reduced serum immunoglobulin levels (Orange et al, 2006).
- Prevention strategies for late infections after HCT, including aggressive prophylaxis strategies, vaccination, and pre-emptive monitoring (Marr, 2012).
- Use of antiviral drugs (eg, acyclovir, valacyclovir, ganciclovir), antibiotics (eg, quinolone), and antifungals (eg, fluconazole) (Marr, 2012).

Natural history of the indicated condition in the population, including mortality and morbidity:

Although infectious risks persist late after HCT, the timing of infection is unpredictable and multiple variables affect the likelihood of infection (Marr, 2012). Bacterial, viral, and fungal infections are common and account for a number of delayed deaths in allogeneic HCT patients (Marr, 2012). Infections typically manifest in the respiratory tract (Marr, 2012). Multiple viruses cause infection later after HCT, including several herpes viruses (eg, cytomegalovirus and varicella zoster virus) and other respiratory viruses such as influenza and adenovirus. These infections can cause severe disease (Marr, 2012).

Important comorbidities:

Bacterial, viral, and fungal infections are common in patients that have undergone allogeneic HCT, and account for a number of delayed deaths (Marr, 2012). Multiple viruses cause infection later after the transplantation, including several herpes viruses (eg, cytomegalovirus and varicella zoster virus) and other respiratory viruses such as influenza and adenovirus; these infections can cause severe disease (Marr, 2012).

Congenital Acquired Immunodeficiency Syndrome (AIDS) with recurrent bacterial infections

Incidence:

The incidence of human immunodeficiency virus (HIV) in children < 15 years has been estimated at 180,000 (110,000 to 260,000) by World Health Organization (WHO) (WHO, 2017).

Prevalence:

Globally the WHO has estimated HIV prevalence at 36.9 (31.1 to 43.9) million persons and 1.8 (1.3 to 2.4) million children < 15 years of age (WHO, 2017). HIV prevalence can vary widely by region and risk group even in a single country (Piot and Quinn, 2013). Sub-Saharan Africa is the most affected continent (prevalence: 15 to < 28%), followed by Eastern Europe and the Caribbean (prevalence: 1.0 to < 5.0%) (Piot and Quinn, 2013). The majority of vertical transmission of HIV occurs at the time of birth. In nonbreastfeeding populations, the rate of vertical transmission of HIV in untreated HIV positive women is estimated at 13 to 39% of pregnancies. Much of this transmission results from intrapartum exposure to maternal bodily fluids (Soilleux and Coleman, 2003). A small percentage (1.5 to 2.0%) of HIV transmission occurs across the placenta (Soilleux and Coleman, 2003).

Demographics of the population in the authorised indication and risk factors for the disease:

Demographics: More than 90% of the world's HIV-infected children reside in sub-Saharan Africa, where mother-to-child-transmission of HIV-1 remains the most important cause of paediatric HIV infection (Buchanan et al, 2014).

Risk factors for the disease: There is a higher in utero and perinatal HIV infection risk in girls than boys (Biggar et al, 2006).

The main existing treatment options:

Main treatment options for congenital HIV with recurrent bacterial infections include symptomatic administration of IVIg to prevent bacterial infections (Orange et al, 2006).

Natural history of the indicated condition in the population, including mortality and morbidity:

It is estimated that 50% of HIV-infected children will die by the age of 2 years without proper care and treatment (Buchanan et al, 2014). HIV infection is accompanied by functional immunodeficiency and loss of mucosal barrier integrity, allowing microbial translocation and driving disease progression. A number of HIV-related opportunistic infections have been documented in the literature, such as those colonising gastrointestinal and vaginal mucosal tissues (Victoriano et al, 2013). Microbial coinfection contributes to the course of disease progression of HIV infection and the development of AIDS-related deaths (Victoriano et al, 2013).

Important comorbidities:

Opportunistic infection frequently sets in when a HIV infected individual is immunocompromised (Victoriano et al, 2013). Loss of mucosal barrier integrity (such as gastrointestinal and vaginal mucosa) allows microbial translocation, causing disease progression. Microbial coinfection contributes to the course of disease progression of HIV infection and the development of AIDS-related deaths (Victoriano et al, 2013).

Measles pre- / post-exposure prophylaxis

Incidence:

Rates of measles vaccine contraindication and incidence of measles in susceptible adults, children and adolescents in whom active immunisation is contraindicated or not advised has not been well studied. During 2023, the worldwide number of reported measles cases was 663,795 corresponding to 91 cases per 1 million population (Minta et al, 2024). In 2023, a total of 2361 cases of measles were reported across the European Union / European Economic Area (EU / EEA), of which 1607 (68%) were laboratory confirmed with infants aged < 1 year the most affected age group (notification rate of 63.6 cases per 1,000,000 population), followed by children aged 1 to 4 and 5 to 9 years (notification rate 49.2 and 22.2 respectively). Among the reported cases, data on vaccination status were available for 2068 cases (88%). Of these cases, 1786 (86%) were unvaccinated, 155 (8%) were vaccinated with 1 dose of measles containing vaccine, 117 (6%) were vaccinated with 2 or more doses, and ten cases (0.5%) were vaccinated with an unknown number of doses. (ECDC, 2023)

Prevalence:

Measles resolves or results to fatal outcomes within days or a few weeks so prevalence is similar to incidence as new cases are immediately followed by an equal number of recoveries or deaths.

Demographics of the population in the proposed indication and risk factors for the disease:

Demographics: Measles is common, particularly in parts of Africa, the Middle East and Asia. A large proportion of measles deaths occur in countries with low per capita incomes or weak health infrastructures that struggle to reach all children with immunisation (WHO, 2025). In EU / EEA, the notification rates ranged from 0 to 92.2 cases per 1,000,000 population with the highest notification rate of 92.2% in Romania. Also, in EU / EEA, measles is slightly more common among males (5.3 cases per 1,000,000 population) than females (5.1 cases per 1,000,000 population). (ECDC, 2023)

Risk factors for the disease: According to the National Vaccine Information Center, individuals at heightened risk for measles include children who are too young to be vaccinated, individuals who have not been vaccinated due to medical or other reasons, those who have not received a second dose of the measles vaccine, and individuals for whom the vaccine failed to elicit a protective immune response. Furthermore, travel to regions where measles is endemic or contact with individuals arriving from these areas increases the likelihood of exposure to the disease. Malnutrition, particularly in children with insufficient vitamin A, compromised immune systems due to HIV / AIDS or other illnesses, and overcrowded living conditions, exacerbate the risk of contracting measles. The vaccine acquired immunity that most mothers pass on to their infants has been found to be much lower and shorter acting than those produced following natural measles infection, placing these infants at higher risk for measles infection. (NVIC, 2025)

The main existing treatment options:

There is no specific antiviral treatment for measles. Management of the condition is supportive including relieving symptoms, making the patient comfortable and preventing complications. (ECDC, 2023; WHO, 2025)

Natural history of the indicated condition in the population, including mortality and morbidity:

Measles spreads through droplets from infected individuals. Symptoms appear 10–14 days after infection, including high fever, runny nose, bloodshot eyes, white spots inside the mouth, and a rash starting on the face and neck spreading downwards. The rashes fade in the order of appearance during the next 3 to 4 days.

Severe measles is more common in malnourished children, particularly those lacking vitamin A or with weakened immune systems due to HIV / AIDS or other illnesses. Serious complications can include blindness, encephalitis (brain swelling), severe diarrhoea with dehydration, and respiratory infections like pneumonia. Mortality from measles is predominantly caused by complicating bacterial infections. (ECDC, 2023; WHO, 2025) In 2023, the EU / EEA reported data on complications for 726 cases (31%). Among these, 140 cases (2%) had no complications. Complications included 561 pneumonia cases, 12 diarrhoea, 4 otitis media cases, and 1 acute encephalitis. Eight cases had unspecified complications. Of the 586 cases with complications, 518 (88%) were unvaccinated. (ECDC, 2023)

Important comorbidities:

Common complications from measles include otitis media, bronchopneumonia, laryngotracheobronchitis, and diarrhea. 1 out of every 1000 measles cases will develop acute encephalitis, which often results in permanent brain damage.1 to 3 out of every 1000 children who become infected with measles will die from respiratory and neurologic complications. Subacute sclerosing panencephalitis is a rare, but fatal degenerative disease of the central nervous system characterised by behavioral and intellectual deterioration and seizures that generally develop 7 to 10 years after measles infection. Risk of subacute sclerosing panencephalitis may be higher for children who contact measles before 2 years of age. (CDC, 2024)

Primary ITP in patients at high risk of bleeding or prior to surgery to correct the platelet count

The age-adjusted prevalence of ITP is estimated to be 9.5 per 100,000 persons in the United States of America (USA) while its annual incidence is estimated to be 2.68 per 100,000 in Northern Europe (Fogarty and Segal, 2007; Michel et al, 2009).

In childhood onset ITP, affected children are young and previously healthy, and in more than 70% of cases, the illness resolves within 6 months. By contrast, adult onset ITP is generally chronic, and the onset is often insidious (Cines et al, 2002).

Demographics of the population in the authorised indications and risk factors for the disease:

Demographics: The mean age of adults at diagnosis in Europe is 50 years and the incidence of ITP increases with age (Michel et al, 2009). In adult-onset ITP, twice as many females are affected than males. In childhood-onset ITP the peak age at diagnosis is approximately 5 years, and occurs equally in male and female patients (Cines et al, 2002).

Risk factors for the disease: Risk factors for the onset of ITP include age; there is an increased incidence of ITP among the elderly (Sarpatwari et al, 2010). In addition, there is a moderate female preponderance, which lessens with increasing age (Sarpatwari et al, 2010). Although familial ITP is clinically rare, a high rate of family history was observed in a registry study (Ku et al, 2013). Genetic variations in several genes (eg, IL-10 and Fc-gamma receptors) may increase an individual's genetic deposition to ITP (Ku et al, 2013).

The main existing treatment options:

The main treatment options for ITP include (Kashiwagi and Tomiyama, 2013):

- IVIg, platelet transfusion, and methylprednisolone in emergency situations.
- Corticosteroids (usually prednisolone) as first-line treatment.
- For corticosteroid-resistant patients, a splenectomy as second-line treatment.
- For refractory ITP patients in whom corticosteroids and splenectomy fail, thrombopoietin receptor agonists (eltrombopag, romiplostim) danazol, azathioprine, vincristine slow infusion, high-dose dexamethasone, methylprednisolone pulse, cyclosporine, rituximab, as third-line treatment.

Natural history of the indicated condition in the population, including mortality and morbidity:

The major cause of fatal bleeding in patients with ITP is intracranial hemorrhage. In the small subgroup of patients with severe thrombocytopenia (platelet count below 20,000 per cubic millimeter), 5-year mortality rates from bleeding range from 2.2% for those younger than 40 years of age to 47.8% for those over 60 years of age (Cines et al, 2002).

Important comorbidities:

Secondary forms of ITP commonly occur in association with systemic lupus erythematosus, antiphospholipid syndrome, immunodeficiency states (immunoglobulin A [IgA] deficiency and common variable hypogammaglobulinemia), lymphoproliferative disorders (CLL, large granular lymphocytic leukemia, and lymphoma), infection with HIV and hepatitis C virus, and therapy with drugs such as heparin and quinidine (Michel et al, 2009). In a study of 1 state in the USA, the prevalence of multiple sclerosis in association with ITP was approximately 25 times the prevalence that would be expected in the general population (Fogarty and Segal, 2007).

Guillain-Barré syndrome

A systematic literature review of the epidemiology of GBS showed that the incidence rates (majority) of GBS reported were between 0.81 and 1.89 per 100,000 per year. Most of the studies included were from Europe and North America where the rates were similar. The majority of studies used the recognised National Institute of Neurological and Communicative Diseases criteria (or a comparable set) and this allowed comparisons to be made between studies (Sejvar et al, 2011).

The global prevalence of GBS has been estimated as 65,000 in 2016 (Vos et al, 2016).

Demographics of the population in the authorised indication and risk factors for the disease:

Demographics: GBS incidence in children 0 to 9 years was estimated at 0.62 cases per 100,000 person-years as compared to 2.66 cases per 100,000 person-years among persons 80 to 89 years of age (Sejvar et al, 2011).

Higher incidence rates have been reported in males compared to females, which is unusual for an autoimmune disease (Hughes and Rees, 1997; Sejvar et al, 2011).

Risk factors for the disease: Risk factors for the development of GBS include advanced age and gender, with a slight predominance in males (Winer, 2014). In addition, 3 quarters of patients describe a triggering infection, usually respiratory or gastrointestinal in nature (the neuropathy typically begins 7 to 10 days afterwards). Other triggering events include surgery and immunisation (Winer, 2014). A number of reports also associate GBS with mycoplasma pneumonia, influenza, and varicella (Winer, 2014). The risk of GBS syndrome after influenza

vaccination in adults is 2 to 5 cases per 1,000,000 vaccinations (Galeotti et al, 2013). An increased risk has also been described after Zika virus infection (Cao-Lormeau et al, 2016).

The main existing treatment options:

Main treatment options for GBS include immune modulation; IVIg or plasma exchange are the mainstays of treatment. However, IVIg is the preferred treatment in most circumstances (Winer, 2014).

Natural history of the indicated condition in the population, including mortality and morbidity:

Sensory symptoms in the legs usually mark the onset of the disease, followed by rapidly progressive distal weakness that soon spreads proximally. Lumbar pain is common (Winer et al, 2014). The prognosis of GBS is usually favorable but it is a serious disease with a mortality of approximately 10% and approximately 20% patients have residual severe disability (Kuwabara, 2004). A 2008 epidemiological study reported 2 to 12% mortality despite Intensive Care Unit management (Alshekhlee et al, 2008). The outcome does not appear to correlate with the severity of the disease at onset (Khan et al, 2010; Rudolph et al, 2008).

Important comorbidities:

GBS is thought to be autoimmune and triggered by a preceding infection in 2 thirds of cases. This infection is most frequently a respiratory or a gastrointestinal infection (Govoni and Granieri, 2001; Hughes and Rees, 1997). The association between antecedent viral, upper respiratory tract, and *Campylobacter jejuni* infections prior to the onset of GBS has been known for many years; however, the suggested link between Zika virus and GBS is more recent (Krauer et al, 2017; Nachamkin et al, 1998).

GBS has also been shown to have links with chronic diseases, including CIDP and subacute demyelinating neuropathy (Winer, 2014).

Kawasaki disease

Incidence:

First described in Japan in 1967 (Kawasaki et al, 1967), the disease is now a leading cause of acquired heart disease in developed countries worldwide (Newburger et al, 2004).

The disease is observed most frequently in Japan, Taiwan and Korea. The highest incidence is in Japan where the frequency is 10 to 20 times higher than in Western countries (Onouchi et al, 2008). The average incidence in Japan reported in a review was 308 cases per 100,000 per year in children aged less than 4 years (Makino et al, 2018). The reported annual incidence in white populations outside the USA is similar to that reported in the USA. In North America, the annual incidence has been reported to range from 7.9 to 21.9 per 100,000 children < 5 years (Sehgal et al, 2015; Singh et al, 2015). Prevalence of Kawasaki disease is not well characterised.

Demographics of the population in the authorised indication and risk factors for the disease:

Demographics: Approximately 85 to 90% of Kawasaki disease cases occur in children aged less than 5 years (Pinna et al, 2008). The disease has rarely been reported in adolescents and adults, most of who were aged between 18 and 30 years. The disease is more common in males than females. Estimates of the male: female ratio range from 1.3:1 to 1.83:1 depending on the country from which the data are reported (Holman et al, 2010).

Although Kawasaki disease has been reported in children from all ethnic and racial backgrounds, it occurs most commonly in Asian children.

Risk factors for the disease: Although significant differences in epidemiological distribution have been observed worldwide, a number of risk factors appear relatively constant (Jamieson and Singh-Grewal, 2013):

- Gender: male predominance (male-to-female ratio between 1.5:1 and 2:1).
- Seasonality: greater incidence in winter and early spring in temperate climates, and in summer for some Asian countries.
- Age: approximately 75% of cases occur in children under 5 years of age.
- Ethnicity: heightened incidence in people of Asian descent, both inside and outside of Asia.
- Genetic predisposition: there is a higher relative risk of Kawasaki disease within families. Siblings of a Kawasaki disease patient are at a 10-fold higher risk of Kawasaki disease compared to the general population. Linkage analysis and genome-wide association studies have identified several single nucleotide polymorphisms that show an association with genetic susceptibility to Kawasaki

disease, such as functional polymorphisms of the FC gamma RIIa locus and the ITPKC gene.

The main existing treatment options:

Acute phase management of Kawasaki disease includes treatment with IVIg, anti-inflammatory and antiplatelet aspirin doses, percutaneous coronary intervention procedures (indicated in patients at high risk of ischemia), and coronary artery bypass surgery (indicated if angiography detects severely occlusive lesions or jeopardised collateral blood supply (Jamieson and Singh-Grewal, 2013). Chronic phase management includes treatment with antiplatelet aspirin doses and systemic anticoagulation therapy with warfarin or low molecular weight heparin in patients with giant or multiple large aneurysms (Jamieson and Singh-Grewal, 2013).

Natural history of the indicated condition in the population, including mortality and morbidity:

Kawasaki disease causes coronary artery abnormalities in 25% of untreated patients, and has surpassed rheumatic heart disease as the leading cause of acquired cardiovascular disease in children in the developed world (Jamieson and Singh-Grewal, 2013). The data are limited but in the USA mortality rate is approximately 1% of affected children. In children less than 1 year, the mortality rate may be greater than 4%. The peak mortality rate occurs 15 to 25 days after the onset of fever. No deaths have been reported in adults to date (Wolff et al, 2007).

Important comorbidities:

No common comorbidities with Kawasaki disease could be identified from the literature.

Chronic inflammatory demyelinating polyneuropathy

Incidence:

The incidence of CIDP is estimated to be from 0.15 to 1.6 per 100,000 individuals / year (Hafsteinsdottir et al, 2016; Laughlin et al, 2009; McLeod et al, 1999).

Prevalence:

Data on the prevalence of CIDP range from 0.8 to 8.9 per 100,000 worldwide (Mahdi-Rogers et al, 2014).

Demographics of the population in the authorised indication and risk factors for the disease:

Demographics: CIDP prevalence increases with age and reaches a peak in the 70 to 79-year age group. Prevalence has been reported to be higher in males as compared to females (Mahdi-Rogers et al, 2014; McLeod et al, 1999).

Risk factors for the disease: Risk factors for the development of CIDP include gender, with a slight male predominance (Bright et al, 2014). CIDP may also develop after bacterial or viral infection, particularly viral hepatitis and post-vaccination (Bright et al, 2014).

The main existing treatment options:

Treatment options for CIDP depend on several variables, such as initial disease severity, age, general health status, and potential contraindications (Ripellino et al, 2014). Current treatments for CIDP include immunomodulating, anti-inflammatory, and immunosuppressive drugs (Bright et al, 2014):

- First line treatments: corticosteroids, IVIg (Bright et al, 2014).
- Standard therapeutic plasma exchange: for rapid removal of circulating autoantibodies, cytokines, immune complexes, and immune cells. Limited chronic use in elderly patients or in patients with multi-organ disease (Ripellino et al, 2014).
- Immunosuppressive drugs: antimetabolites (eg, azathioprine, methotrexate, mycophenolate mofetil); alkylating agent (eg, cyclophosphamide); monoclonal antibody (eg, rituximab, natalizumab); ciclosporin A (Ripellino et al, 2014).

Natural history of the indicated condition in the population, including mortality and morbidity:

CIDP follows a progressive, monophasic or relapsing remitting course with clinical signs being proximal and distal weakness (usually symmetrical), sensory involvement (numbness), and are flexia. Nerve conduction in CIDP patients may exhibit prolonged distal motor latency, slowed conduction velocity, partial conduction block and delayed or absent F-wave (Bright et al, 2014).

In a study of 100 patients with CIDP followed up for 6 years, 9 patients had died as a consequence of their neurologic deficit (Bouchard et al, 1999).

Important comorbidities:

No common comorbidities with CIDP could be identified from the literature.

Multifocal motor neuropathy

Incidence and Prevalence

Incidence of MMN has not been well characterised due to its rarity and challenges in diagnosis. Prevalence of MMN has been reported as 0.5 to 1.5 per 100,000 persons (Cats et al, 2010; Deenen et al, 2015; Loescher et al, 2018; Mahdi-Rogers et al, 2014).

Demographics of the population in the authorised indication and risk factors for the disease:

Demographics: Prevalence of MMN is reported to be nearly 3 times higher in males as compared to females and the mean age of onset has been reported as 40 years (Cats et al, 2010).

Risk factors for the disease: Risk factors for the development of MMN include male gender (Cats et al, 2010).

The main existing treatment options:

IVIG is the most frequently used treatment in MMN. Subcutaneous Ig has also been utilised and provides an alternative that for some patients may be more convenient and provide fewer side effects. Plasma exchange and steroid treatment can also be used for treatment although their efficacy in MMN patients has not been well characterised. Other lesser utilised therapies include cyclosphosphamide, rituximab, mycophenolate mofetil, β-interferon, cyclosporine, azathioprine, and infliximab, although clinical trials have not conclusively shown these to be effective (Lawson and Arnold, 2014).

Natural history of the indicated condition in the population, including mortality and morbidity:

MMN typically presents with asymmetric weakness in single peripheral nerves and slowly progresses to a more confluent and segmental pattern (Lawson and Arnold, 2014).

The majority of patients diagnosed with MMN maintain their activities of daily living despite ongoing progressive symptoms (Erdmann et al, 2010). Fatal outcomes have only been reported rarely.

Important comorbidities:

No common comorbidities with MMN could be identified from the literature.

Important comorbidities in the general population

Privigen contains traces of IgA, which seldom provoke anaphylaxis in IgA deficient patients with anti-IgA antibodies. This is a known risk in patients administered IVIg products, and the risk is not considered to be any greater with Privigen. It is adequately described in the Precautions section of the Summary of Product Characteristics (SmPC).

Part II: Module SII - Nonclinical part of the safety specification

There is a history of safe use and proven efficacy of IgG formulations in humans. Considering this and due to the xenoreactivity of human IgG, Privigen was not examined in the full battery of pharmaco-toxicology studies. In addition, the sole excipient in Privigen, L-proline, is not a novel excipient for parenteral use, and is 1 of the 3 excipients used in Sandoglobulin® Liquid, a liquid IVIg formulation previously developed by CSL Behring (CSLB). For these reasons, the nonclinical programme with Privigen was limited to 2 local tolerance studies in rabbits, 1 safety pharmacology study in rats, and several other safety studies with L-proline. Safety studies with L-proline were supplemented with study results of the Sandoglobulin Liquid additive mixture (containing L-isoleucine and nicotinamide in addition to L-proline).

L-proline is known to be well tolerated in humans, and there is a long history of safe administration as a medicinal product in high doses for parenteral nutrition, also indicated for premature and / or newborn babies.

Overall, Privigen was well tolerated upon different routes of administration (IV and subcutaneous), and the excipient L-proline demonstrated an acceptable toxicity profile. A summary of key nonclinical findings and their relevance to humans is outlined below.

Key safety findings from nonclinical studies and relevance to human usage:

Toxicity

Key safety findings (from nonclinical studies)	Relevance to human usage
Single and repeat-dose toxicity Due to the formation of antibodies to foreign protein in animals, meaningful or scientifically sound data on safety cannot be expected from preclinical studies involving long-term exposure of laboratory animals to human immunoglobulins. As such studies are neither feasible nor relevant, none were performed. Daily IV dosing of L-proline in 5-day and 28-day toxicity studies in rats up to the maximum daily doses that could be infused in this model showed no overt toxicity. The NOAEL of L-proline in both studies was the high dose tested (1449 mg/kg bw/day). Thus, a safety margin of 5 relative to the maximum daily human dose used in clinical studies with Privigen (1 g IgG/kg bw applied on 2 consecutive days) or a safety margin of 2.5 relative to the maximum single human dose used with	Due to the fact that immunoglobulins are of human origin, and are catabolised in the same manner as the patient's endogenous immunoglobulins, no toxicity is expected. Repeated-dose toxicity studies with the sole excipient L-proline performed in 2 species did not reveal any toxicologically important findings.

Key safety findings (from nonclinical studies)	Relevance to human usage
IVIg in indications such as Kawasaki disease (2g IgG/kg bw) was obtained. In the 7-day and 28-day repeated-dose toxicity studies in dogs, daily IV L-proline doses of up to 4350 mg/kg bw showed no overt toxicity. The NOAEL was considered to be 4350 mg/kg. Thus, a safety margin of 15 relative to the maximum human dose used in clinical studies with Privigen could be established. The maximum duration of the preclinical studies (28 days) was justified in view of the short half-life of L-proline and the dosing regimens of Privigen in clinical use (1g IgG/kg bw given daily on 2 consecutive days or 0.2 g bw giving IgG/kg bw every 3 or 4 weeks).	
Reproductive and developmental toxicity Physiological constituents of the human blood immunoglobulins are not expected to induce adverse effects on reproduction or the fetus. No meaningful results can be expected from animal reproduction studies due to the heterologous nature of the protein for animals. For L-proline, segments I (fertility and early embryonic development) and III (pre- and post-natal development, including maternal function) reproductive toxicity data have not been generated. Only teratogenicity (segment II) data for L-proline have been generated by CSLB in view of: • The established nature of the nonessential amino acid L-proline, endogenously bioavailable in humans and used extensively at similar maximum doses in parenteral nutritional products for humans, including newborns. • The lack of treatment-related histopathological findings in reproductive tissue of both sexes in the two 28-day toxicity studies in rats (epididymides; mammary gland; ovaries; prostate; seminal vesicles; testes, uterus; vagina) treated at the highest dose level and sacrificed on the last day of the studies. Segment II data were generated by CSLB for L-proline alone, and in combination with L-isoleucine and nicotinamide, respectively. The latter were generated during the development of Sandoglobulin Liquid (another liquid IVIg product of CSLB) and serve as supporting information. In the study assessing L-proline alone at daily doses of 1449 mg/kg bw (ca. 5 times higher than those applied in the clinical studies) no teratogenic or embryotoxic effects were found. This dose represents a NOEL.	There is no evidence for reproductive toxicity of L-proline. As immunoglobulins are of human origin and are catabolised in the same manner as the patients' endogenous immunoglobulins, reproductive toxicity is not expected.

Key safety findings (from nonclinical studies)	Relevance to human usage
Immunoglobulins are excreted into the milk and may contribute to the transfer of protective antibodies to the neonate.	
Genotoxicity and carcinogenicity No evidence exists, that genotoxicity or mutagenicity can be induced by human plasma proteins. Furthermore, it is unlikely that meaningful or realistic data could be obtained from studies involving long-term exposure of laboratory animals to human plasma proteins. Therefore, it is not scientifically sensible or relevant to undertake carcinogenicity testing of immunoglobulins. The battery of genotoxicity studies performed by CSLB (comprising in vitro tests as well as induction of micronuclei in the bone marrow of mice treated with a single injection) for L-proline showed no positive genotoxicity findings. In addition, L-proline did not show a carcinogenic potential in hamsters (Thamavit et al, 1994).	Based on nonclinical data; there is no evidence for a genotoxic or carcinogenetic potential of L-proline. Due to the fact that immunoglobulins are of human origin and are catabolised in the same manner as the patient's endogenous immunoglobulins, genotoxicity and carcinogenicity is not expected.
Local tolerability In a study in rabbits, local tolerance of Privigen after SC application was assessed to examine whether this slightly acidic product (pH of 4.8) would be equally well tolerated as Beriglobin®P, a marketed SCIg product formulated at a near physiological pH (approx. 6.8). Local tolerance of Privigen after SC administration was similar to that of saline and better than for Beriglobin®. In addition, Privigen showed acceptable local tolerance after IV, paravenous and intraarterial application in a second study in rabbits.	Based on nonclinical data, no treatment-related local reactions are expected.
Thrombogenicity No nonclinical studies were performed to investigate the thromboembolic potential of Privigen.	No nonclinical data are available. However, there is clinical evidence of an association between IVIg administration and thromboembolic events. Therefore, caution should be exercised in prescribing and infusing IVIg in obese patients and in patients with pre-existing risk factors for thrombotic events; in patients at risk of thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

bw = bodyweight; CSLB = CSL Behring; IgG = immunoglobulin G; IV = intravenous; IVIg = intravenous immunoglobulin; NOAEL = no observed adverse effect level; NOEL = no observed effect level; SC = subcutaneous; SCIg = subcutaneous immunoglobulin

Safety pharmacology

Key Safety findings (from nonclinical studies)	Relevance to human usage usage
Safety pharmacology IV administration of Privigen to rats caused only moderate hypotension that was within the same range as caused by Sandoglobulin Liquid. Results of studies with this animal model correlate with the transient acute inflammatory reactions which may occur during IV infusion of IgG products into humans (Spycher et al, 1999). L-proline is described as an excitatory amino acid based on in vitro and in vivo findings (intracranial or chronic application). In a 5-day Irwin test with IV application of L-proline during 7 hours/day, no significant neurological effects at doses of L-proline up to 1449 mg/kg bw/day were found, except for a slight increase of rectal body temperature of cumulated doses of L-proline after 5 days of treatment. The absence of acute neurological effects was confirmed by studies in adult and juvenile rats with SC application of 2 and 1.9 g L-proline, respectively, leading to considerably higher C_{max} values than maximally obtained with IV infusions (up to 15 mmol/L vs up to 4 mmol/L). In a water maze study in juvenile rats, L-proline was administered to animals at daily doses up to 4000 mg/kg using an application scheme relevant for Privigen administrations to human individuals (daily application during 5 succeeding days or weekly applications). Animals of all test groups showed a successful acquisition of reference memory and a good performance in the testing of reference and working memory. There were no indications of any negative effects on acquisition of reference memory, reference or working memory by any of the different pre-treatments.	Based on nonclinical data, aside from moderate hypotension, no cardiovascular treatment-related effects and no acute neurological treatment-related effects are to be expected.
Interaction with other medicinal products Interactions with other medical products are not expected due to the nature of human plasma proteins constituents of Privigen. In spontaneous AE reporting of marketed product, no evidence for interaction with other medicinal products has been observed.	Privigen is an endogenous human plasma protein, and therefore is not subject to metabolism by cytochrome P450 isoenzymes, excretion or PK interactions exhibited by many low molecular weight compounds. No drug interactions are expected.

AE = adverse event; bw = bodyweight; IgG = immunoglobulin G; IV = intravenous; PK = pharmacokinetic; SC = subcutaneous

Other toxicity-related information or data

There are no other toxicity-related information or data for Privigen. There is no need for additional preclinical studies based on above findings.

Part II: Module SIII - Clinical trial exposure

In completed studies, a total of 450 subjects (101 PID, 114 ITP, 235 CIDP) were exposed to Privigen, receiving a total of 3248 infusions (1162 PID, 207 ITP, 1879 CIDP).

Table SIII-1: Demographic data of all 450 subjects exposed to Privigen in completed clinical studies

	PID Pivotal Study	PID Extension (new)[a]	PID Japan	ITP Pivotal Study	ITP PMC Study	CIDP PRIMA Study	CIDP PATH Study	Total
Gender; No. subjects								
Number	80	55 (10)	11	57	57	28	207	450
Female	34	29 (7)	3	34	37	10	76	201
Male	46	26 (3)	8	23	20	18	131	249
Age class, years; No. subjects								
3 to < 12	19	13 (0)	1	-	-	-	-	20
12 to < 16	12	8 (2)	1	1	-	-	-	16
16 to < 65	45	30 (7)	8	54	55	18	150	337
≥ 65	4	4 (1)	1	2	2	10	57	77
Race / Ethnic group; No. subjects								
Asian	-	-	11	-	-	-	17	28
Black / American	6	5 (0)	-	-	-	-	-	6
Caucasian	62	41 (10)	-	57	57	28	187	401
Hispanic	12	9 (0)	-	-	-	-	-	12
Others	-	-	-	-	-	-	3	3

CIDP = chronic inflammatory demyelinating polyneuropathy; ITP = primary immune thrombocytopenia; PATH = polyneuropathy and treatment with Hizentra; PID = primary immunodeficiency syndrome; PMC = post-marketing commitment; PRIMA = Privigen impact on mobility and autonomy

[a] In the PID extension study 45 subjects from the pivotal PID study were further treated and 10 new subjects were enrolled.
* Of note: in the CIDP PATH study 1 subject who was American Indian or Alaska Native, was categorised as 'Caucasian'
Source: CSR ZLB03_002CR [5.3.5.2-1] Tables XI, XIV; CSR ZLB05_006CR_CSR Table 11.2.5.A; CSR ZLB03_003CR [5.3.5.2-2] Tables IX, XII; CSR IgPro10_3001 [5.3.5.2.4 Listing 16.2.2.1] CSR IgPro10_4001 [Table 14.1.2, Listing 16.2.4.1]; CSR IgPro20_3003 [Table 14.2.4.2.1 Listings 16.2.4.1.1]; CSR IgPro10_3004 [Table 14.1.4.1.1 Listings 16.2.4.1].

Table SIII-2: Privigen exposure in completed clinical studies by dose, subject numbers and number of infusions

Study	Dose in g/kg bw	Subject exposure (Subject number)	Total number of infusions
PID pivotal and extension study	200-888 mg/kg bw every 3-4 weeks	90	1119
PID Japan study	137.7-556.0 mg/kg bw every 3-4 weeks	11	43
ITP study ZLB03_003CR	2 g/kg bw, divided over 2 subsequent days	57	114
ITP PMC study IgPro10_4001	1 g/kg bw in 21 subjects 2 g/kg bw in 36 subjects	57	93
CIDP study IgPro10_3001 (PRIMA study)	2g/kg bw, divided over 2-5 days followed by 1g/kg bw every 3 weeks[a]	28	259
CIDP study IgPro20_3003 (PATH study)	2g/kg bw, divided over 2-5 days followed by 1g/kg bw every 3 weeks	207	1620

bw = bodyweight; CIDP = chronic inflammatory demyelinating polyneuropathy; ITP = primary immune thrombocytopenia; PATH = polyneuropathy and treatment with Hizentra; PID = primary immunodeficiency syndrome; PMC = post-marketing commitment; PRIMA = Privigen impact on mobility and autonomy
[a] There have been no hemolysis cases reported with Privigen CIDP maintenance treatment of 1 g/kg bw

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Table SIV.1-1: Exclusion criteria that are not proposed to remain as contraindications or missing information

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication or missing information
Any polyneuropathy of other causes (for CIDP study).	To not interfere with the efficacy analyses of the study.	Does not imply an additional risk for the subjects.
Any other disease that has caused neurological symptoms (for CIDP study).	To not interfere with the efficacy analyses of the study.	Does not imply an additional risk for the subjects.
Severe diseases and conditions likely to interfere with evaluation of the study eg, current malignancies, cardiac insufficiency, chronic kidney disease stage IV and V, known bleeding disorders, severe skin disease at the planned injection sites, alcohol, drug or medication abuse.	To not interfere with the efficacy or safety analyses of the study.	The risk has to be balanced against the benefits on an individual basis.
Treatment with immunosuppressants before enrolment.	To not interfere with the efficacy analyses of the study.	Does not imply an additional risk for the subjects.
Creatinine > 1.5 ULN, Hemoglobin < 10 g/L	To not interfere with the efficacy analysis of the study (impaired renal function may lead to significant protein loss, including loss of the administered IgG). Increased creatinine may indicate chronic renal impairment, a risk factor for acute renal failure with IVIg. Low hemoglobin may be a risk factor for hemolytic anemia.	Does not imply an additional risk for the subjects. Hemolytic anemia and acute renal failure are sufficiently addressed in the warnings and precautions section in the Privigen label.
Hyperprolinaemia (Type I or II)[a]	To not interfere with the safety analyses of the study.	The risk has to be balanced against the benefits on an individual basis

Criteria	Reason for being an exclusion criterion	Justification for not being a contraindication or missing information
Pregnancy, nursing mother; female with childbearing potential without using contraception	Common practice to not include this patient group	Clinical practice has not revealed any risk for mother or child with the use of IgG, however, data are limited.

CIDP = chronic inflammatory demyelinating polyneuropathy; EU = European Union; ULN = upper limit normal; USA = United States of America

[a] This exclusion criterion is a contraindication in some countries (including all EU member states and the USA) or addressed in the warnings and precautions section in the Privigen label in other non-EU countries (eg, Canada) according to the Health Authority approvals.

The safety-relevant parameters of the above exclusion criteria are adequately addressed in the product labeling and reference safety information, and are either mentioned as absolute contraindications or as relevant warnings / precautions.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Clinical trial development programmes are unlikely to detect the following types of adverse reactions due to well-known inherent limitations. Limitations of the Privigen clinical trial development programme are summarised below.

Limitations of the clinical development programme

Ability to detect adverse reactions	Limitation of trial programme	Discussion of implications for target population
Which are rare; it may be appropriate to choose other ADR frequencies.	A total of 450 subjects were exposed to Privigen over the whole clinical development programme.	ADRs with a frequency greater than 1 in 50 with 95% confidence interval could be detected if there were no background incidence.
Due to prolonged exposure	Not applicable	Not applicable
Due to cumulative effects	Not applicable	Not applicable
Which have a long latency	Not applicable	Not applicable

ADR = adverse drug reaction

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.3-2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Females who are pregnant, breast feeding or planning a pregnancy during the course of the study were excluded from the studies, and females who were of child bearing potential must have had a negative pregnancy test at screening. The exclusion of pregnant or lactating women (as well as women planning a pregnancy during the course of a clinical study) is not product specific, but a general ethical requirement for the vast majority of clinical trials. Clinical experience with immunoglobulins suggests that no harmful effects on the course of the pregnancy or on the fetus are to be expected (Caress et al, 2010; Radder et al, 2004).
Breastfeeding women	
Children & Elderly - Patients < 3 years of age or > 70 years of age (PID studies); Patients < 12 years of age or > 65 years of age (ITP study); Patients < 18 years of age (CIDP study)	Age was not defined as an exclusion criterion, but an inclusion criterion was defined as 3 to 70 years in the PID study, 12 to 65 years in the ITP study and ≥ 18 years in the CIDP and the ITP PMC studies. Although there was no clinical study experience of Privigen in these patient age groups, Privigen is indicated for use and has been used post-market in all age groups; its use in these patient groups is not considered to represent a safety concern due the well-established safety profile of IVIg. Appropriate wording in the Precautions section of the Company Core Safety Information has been included to advise on the extent of clinical experience in special populations with regards to age.
Patients with relevant comorbidities:	
• Patients with suspected hypersensitivity, severe side effects to immunoglobulin therapy, selective IgA deficiency or antibodies to IgA	Patients with known or suspected severe hypersensitivity or previous evidence of severe side effects to immunoglobulin therapy or other blood products were excluded from the 5 studies. In addition, in the PID study, patients with known selective IgA deficiency or antibodies to IgA were excluded. Hypersensitivity to product constituents is a common exclusion criterion, regardless of medicinal product. Appropriate wording in the contraindications and precautions sections of the product information has therefore been included in order to exclude these patients and provide further information in relation to anaphylaxis.
• Patients with a history of migraine, cardiac insufficiency or heart failure or positive direct Coombs' test	Patients with underlying history of migraine may be at greater risk for developing aseptic meningitis syndrome following IVIg therapy (APIIEG, 2009). Patients' positive

CCI [redacted]

Type of special population	Exposure
	for direct Coombs' test are indicative of an underlying hemolysis, and therefore treatment with IVIg may exacerbate this condition (Copelan et al, 1986; Misbah et al, 1993; Thomas et al, 1993). In addition, patients with underlying cardiac insufficiency, cardiomyopathy, significant cardiac dysrhythmia requiring treatment, unstable or advanced ischemic heart disease, congestive heart failure, severe hypertension or hyperviscosity are at greater risk of developing thromboembolic events (Brown and Ballas, 2003; Dalakas and Clark, 2003; Dalakas, 1994; Debes et al, 2007; Paran et al, 2005; Stangel et al, 2003).
Other Indications not studied in the clinical development programme	In addition to the disorders studied in the 6 clinical trials (PID, ITP, and CIDP), Privigen has been approved and used for the indications 'myeloma or CLL with severe secondary hypogammaglobulinemia and recurrent infections', 'children with congenital AIDS and recurrent infections', 'GBS', 'Kawasaki disease', and 'allogeneic bone marrow transplantation'. It is not considered that there would be a safety concern with the use of Privigen in these patient populations, as there is established use of other IVIg products in these indications, including CSLB's Sandoglobulin / Carimune, which was marketed in many countries worldwide and still is in some countries.

AIDS = acquired immunodeficiency syndrome; CIDP = chronic inflammatory demyelinating polyneuropathy; CLL = chronic lymphocytic leukemia; CSLB = CSL Behring; GBS = Guillain-Barré syndrome; IgG = immunoglobulin G; ITP = primary immune thrombocytopenia; IVIg = intravenous immunoglobulin; PID = primary immunodeficiency syndrome; PMC = post-marketing commitment

Part II: Module SV – Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

To optimally reflect the dosage regimens described in the approved SmPC and standard medical practices, CSL Behring is using 12 doses per year for the patient-year calculations based on an estimated standard dose of 30 g/dose.

SV.1.2 Exposure

Cumulatively, since 2008 (year of first launch), CCI kg have been sold worldwide. Using the assumptions provided in SV.1.1 this corresponds to CCI estimated standard doses, ie, an estimated total of CCI patient-years.

CCI [redacted]

Table SV.1.2-1: Cumulative post-marketing sales for Privigen (in kg)

Time Period	2008 to 25 October 2011[a]	26 October 2011 to 31 December 2025[b]	Cumulative period February 2008 to 31 December 2025
Sales volume (per kg)	CCI	[redacted]	[redacted]

[a]Breakdown of sales data by country is not available for this time period.

[b]Sales data in g by country is presented in Table SV.1.2-2 for the period 26 October 2011 to 31 December 2025.

Table SV.1.2-2: Sales volumes for Privigen (in g) from 26 October 2011 to 31 December 2025 broken down by country

	Sales volumes in g
Countries	
EEA Countries	
Austria	CCI
Belgium	CCI
Bulgaria	CCI
Croatia	CCI
Cyprus	CCI
Czech Republic	CCI
Denmark	CCI
Estonia	CCI
Finland	CCI
France	CCI
Germany	CCI
Greece	CCI
Hungary	CCI
Iceland	CCI
Ireland	CCI
Italy	CCI
Lichtenstein	CCI
Luxembourg	CCI
Malta	CCI
Netherlands	CCI
Norway	CCI
Poland	CCI
Portugal	CCI

CCI [redacted]

	Sales volumes in g
Countries	
Romania	CCI
Slovakia	CCI
Slovenia	CCI
Spain	CCI
Sweden	CCI
United Kingdom	CCI
Non-EEA Countries	
Algeria	CCI
Andorra	CCI
Argentina	CCI
Australia	CCI
Azerbaijan	CCI
Bahrain	CCI
Barbados	CCI
Bolivia	CCI
Brazil	CCI
Brunei	CCI
Canada	CCI
Chile	CCI
Costa Rica	CCI
Colombia	CCI
Dominican Republic	CCI
Ecuador	CCI
Egypt	CCI
El Salvador	CCI
Guadeloupe	CCI
Guatemala	CCI
Guyana	CCI
Honduras	CCI
Hong Kong	CCI
Indonesia	CCI
Iran	CCI
Iraq	CCI
Israel	CCI
Jamaica	CCI
Japan	CCI

CCI

	Sales volumes in g
Countries	
Jordan	CCI
Kuwait	CCI
Lebanon	CCI
Macedonia	CCI
Malaysia	CCI
Martinique	CCI
Mexico	CCI
Moldova	CCI
Morocco	-
New Caledonia	CCI
New Zealand	CCI
Nicaragua	CCI
Oman	CCI
Pakistan	CCI
Panama	CCI
Paraguay	CCI
Peru	CCI
Philippine Republic	CCI
Puerto Rico	CCI
Qatar	CCI
Russia	CCI
Réunion	CCI
Saint Barthelemy	CCI
Saint Martin	CCI
San Marino	CCI
Saudi Arabia	CCI
Serbia	CCI
Singapore	CCI
South Africa	CCI
Sri Lanka	CCI
Sudan	CCI
Switzerland	CCI
Taiwan	CCI
Thailand	CCI
Trinidad	CCI
Tunisia	CCI

	Sales volumes in g
Countries	
Turkey	CCI
UN	CCI
USA	CCI
Uruguay	CCI
Uzbekistan	CCI
United Arab Emirates	CCI
Vatican	CCI
Yemen	CCI

EEA = European Economic Area; UN = United Nation; USA = United States of America

There are no available data regarding nonstudy post-authorisation exposure categorised by age group or gender, indication or administered doses.

Post-authorisation off-label use

IVIG are a biologic product originally developed to treat immunocompromised patients. In the past decades, there has been increased utilisation of IVIg in autoimmune conditions. Shemer et al (2018) conducted an observational, retrospective study involving all patients who received IVIG from 2007 through 2015. Subjects were classified into 5 groups according to the indication for treatment. The objectives of the study were to evaluate the clinical use of IVIg in the largest tertiary medical center in Israel and to determine top uses, estimate off-label usage, and assess consumption of this blood product. A total of 1117 patients were identified. The mean (±standard deviation) ages of adults and children were 55 ± 17 and 8 ± 7 years, respectively. Most common indication for treatment were immune-mediated conditions (54%), followed by secondary immunodeficiency (28%), primary immunodeficiency (10%), infections (4%), and miscellaneous (4%). The main immune-mediated conditions treated were hematologic disorders (305 patients, 27%), neurologic disorders (219 patients, 20%), and rheumatologic conditions (79 patients, 7%).

Fifty-six percent of the IVIG infusions were given for off-label Food and Drug Administration indications. The authors concluded that the study demonstrated that immune-mediated conditions represent the majority of indications for treatment with IVIG. They observed a 417% increase in IVIG administration (g) over time, attributed mainly to autoimmune diseases. Many indications are still off-label according to Food and Drug Administration recommendations.

The 3rd National Ig Databases Report of the British NHS showed that neurological indications account for 42% of the global IVIg use, followed by PID (33%) and haemato-oncology (18%) (Sewell et al, 2014).

Off-label use occurs commonly in medical practice; however, this is usually by physicians using their medical judgment and is considered the standard of care for some conditions. CSLB continues to monitor adverse events in case reported with off-label use. It should be noted that CSLB does not endorse or promote the use of Privigen in off-label indications, or outside of the intended use as per the current approved label.

Part II: Module SVI - Additional European Union requirements for the safety specification

Potential for misuse for illegal purposes

As immunoglobulins are normal constituents of the human body and also L-proline does not have a potential for dependency, no potential misuse for illegal purposes can be foreseen for Privigen.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial Risk Management Plan submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the Risk Management Plan

Reason for not including an identified or potential risk in the list of safety concerns in the Risk Management Plan (RMP):

The 'identified' and 'potential' risks of Privigen in the initial RMP, version 1.4, dated 18 February 2008 were re-characterised in the context of grouped medical concepts (rather than individual adverse drug reactions in the subsequent versions of the RMP up to the current version in a manner which allows implementation of meaningful risk minimisation strategies. The re-characterised risks represented the current knowledge of the safety profile of Privigen since the first launch in 2008, in relation to the risks which are currently known to the pharmacological class of IVIg products. In the subsequent sections, the characterised risks are explained in detail.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the Risk Management Plan

The following risks were identified in the first approved Privigen RMP, version 1.4, dated 18 February 2008.

Important Identified Risks:

Undesirable effects (by decreasing frequency):

- Headache (very common);
- Nausea, vomiting, chills, fatigue, and pyrexia / fever (common).

Important Potential Risks:

Undesirable effects with frequency 'uncommon', which are regarded signals, whose causal association to IgPro10 has not been confirmed and whose medical relevance is often inconclusive (single Medical Dictionary for Regulatory Activities Preferred Terms are listed, sorted by System Organ Class):

- Anaemia, anisocytosis (Blood and lymphatic system disorders);
- Dizziness, head discomfort, somnolence, tremor (Nervous system disorders);
- Dyspnoea (Respiratory, thoracic and mediastinal disorders);
- Diarrhoea (Gastrointestinal disorders);
- Hyperbilirubinaemia (Hepatobiliary disorders);
- Pruritus, skin disorder (Skin and subcutaneous tissue disorders);
- Back pain, neck pain, pain in extremity, musculoskeletal stiffness (Musculoskeletal and connective tissue disorders);
- Proteinuria (Renal and urinary disorders);
- Chest pain, general symptom, asthenia, influenza like illness, hyperthermia, pain (General disorders and administration site conditions);
- Bilirubin conjugated increased, blood bilirubin unconjugated increased, Coombs direct test positive, Coombs test positive, blood lactate dehydrogenase increased, hematocrit decreased, alanine aminotransferase increased, aspartate aminotransferase

increased, blood creatinine increased, blood pressure decreased, blood pressure increased, body temperature increased, hemoglobin decreased (Investigations).

Missing information:

The information available from clinical studies on the safety of IgPro10 comprises of 19 children (age 3 to < 12 years) and 13 adolescents (age 12 to < 16 years). Information on the safety could although be broadened with a focus on neurological effects in the paediatric population, especially in the population where the highest single dose of Privigen is used (ie, Kawasaki disease).

Specific safety information is missing in the following indications (because specific clinical data is not required by the Clinical Trial-Guideline):

- Myeloma or chronic lymphocytic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections;
- Children with congenital AIDS and recurrent infections;
- Guillain-Barré syndrome;
- Kawasaki disease;
- Allogeneic bone marrow transplantation.

SVII.2 New safety concerns and reclassification with a submission of an updated Risk Management Plan

There have been no new safety concerns since the previous RMP.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

Important Identified Risk 1: Aseptic meningitis syndrome

Important Identified Risk	**Aseptic meningitis syndrome** Noninfectious meningitis (SMQ) narrow
Potential Mechanism	The mechanism through which IVIg administration causes meningeal irritation and inflammation is not clear (Hopkins and Jolles, 2005). However, it may be due to the following: • An allergic hypersensitivity reaction caused by direct entry of the IVIg preparation into the CSF (Sekul et al, 1994). • Reaction to stabilising products in the preparation, cytokine release triggered by the IVIg therapy or cerebrovascular sensitivity (Sekul et al, 1994). • The increased susceptibility to developing aseptic meningitis syndrome in patients with a history of migraines suggests increased sensitivity of meningeal vasculature to exogenous IgG (Sekul et al, 1994). In acute migraine, various circulating chemicals (eg, serotonin, histamine, catecholamines, cytokines, and prostaglandins) may affect intracranial vasculature. Some of these chemicals may be present in the IVIg preparations or their production may be triggered by the IVIg (Sekul et al, 1994). Ig dimers in IVIg treatments may also play a role (Berg and Fuellenhals, 2016)
Evidence source	AMS is a known class effect of IVIg products. Cases have been received from multiple sources including case reports from clinical trials, post-marketing, and literature. There have been reported cases with IVIg which provided evidence of a causal association. The evidence sources indicate that AMS has an impact on patients in terms of severity / seriousness. Although it is primarily a reversible self-limiting condition, AMS is considered an important identified risk for the class of IVIg products.

Important Identified Risk	**Aseptic meningitis syndrome** Noninfectious meningitis (SMQ) narrow
Characterisation of the risk	AMS is a known class effect of IVIg therapy. In the literature, reported incidence ranged from 0 to 17% (Colovic et al, 2003; Schiavotto et al, 1993; Sekul et al, 1994). AMS may be considered a syndrome with a number of possible etiologies, but is most commonly caused by enteroviral infections in the healthy population (Kumar, 2005; Lee and Davies, 2007). AMS may also be due to a noninfectious drug cause, and the background incidence of AMS in this situation is not known. A cumulative total of 805 post marketing cases (721 for Privigen, 84 for generic IVIg) of AMS were identified (DLP of 31 December 2025) and reported the following 945 AEs relevant to AMS: Meningitis aseptic (695), Photophobia (140), Meningitis (53), Meningism (31), Meningeal disorder (19), Meningitis chemical (3), Meningitis noninfective (2), and 1 each of Meningoradiculitis and Kernig's sign. These reports of AMS are qualitatively and quantitatively in line with the general scientific knowledge of this ADR with IVIg products. The majority (877/945) of AEs relevant to AMS were serious. Of the 945 reported AEs, 782 were assessed by CSL Behring as related, 24 as not related and for 139 AEs causality was not assessable. At the DLP, the outcome for the 945 reported AEs was as follows: resolved (462), not reported / unknown (351), resolving (91), not resolved (27), resolved with treatment (7), fatal (4), and resolved with sequelae (3). The 4 fatal events included Meningitis aseptic (3) and Photophobia (1) which were reported in 4 cases. Causality for 2 AEs of Aseptic meningitis was unassessable due to insufficient information, but the remaining AE was assessed as related as causality could not be excluded. However, this case had limited information regarding temporal relationship, patient risk factors, dosing details, and IVIg brand. Causality for Photophobia was unassessable however multiple drug usage and the comorbid conditions could be an important alternative explanation for the event. Additionally, 1 case from clinical trials was identified (frequency 0.2%). The clinical trial case report was serious. No deaths were reported from clinical trials. Aseptic meningitis is one of the most common inflammatory disorders of the meninges (Kumar, 2005). The most common symptoms are headache, fever, myalgias, malaise, chills, sore throat, abdominal pain, nausea, vomiting, photophobia, stiff neck, and drowsiness (Kumar, 2005). Occasionally children may exhibit altered consciousness in the form of confusion, drowsiness or visual hallucinations (Kumar, 2005). Severe meningeal irritation may result in the patient assuming the tripod position with the knees and hips flexed, neck extended and arms brought back to support the thorax (Kumar, 2005). The clinical disease observed in patients with aseptic meningitis syndrome can vary with the host's age and underlying immune status, and can span the spectrum of an asymptomatic CSF pleocytosis to an illness causing neurological impairment (Irani, 2008). Despite this heterogeneity, most patients with aseptic meningitis present with fever accompanied by complaints of headache, stiff neck, malaise, anorexia, and vomiting (Irani, 2008).

Important Identified Risk	**Aseptic meningitis syndrome** Noninfectious meningitis (SMQ) narrow
Risk factors and risk groups	Risk factors for the onset of aseptic meningitis syndrome include the following: • Children with autoimmune diseases appear to be predisposed to developing aseptic meningitis syndrome following IVIg therapy (Caress et al, 2010). • The vast majority of children who develop aseptic meningitis syndrome following IVIg are treated for ITP (Hamrock, 2006). • Rapid infusion rate (AAAAI, 2010; Hopkins and Jolles, 2005). • Repeated IVIg infusion (AAAAI, 2010). • History of headache and migraine (Hamrock, 2006; Hopkins and Jolles, 2005; Scribner et al, 1994; Sekul et al, 1994). • In persons with community-acquired meningitis, aseptic meningitis is significantly more common than bacterial meningitis; 96% of children with CSF pleocytosis have aseptic meningitis (Bamberger, 2010). Seasonality is important in predicting the likelihood of aseptic meningitis syndrome, because most enteroviral and arboviral infections occur in the summer or autumn in temperate climates (Bamberger, 2010).
Preventability	Consensus recommendations from the Immunoglobulins in Immunology Expert Group (APIIEG, 2009) recommend that 'symptoms may be reduced by pre-medication with an analgesic or a nonsteroidal anti-inflammatory and antihistamine and by slowing the rate of administration'. As with headache, ensuring that the patient is well hydrated may also reduce the incidence of this known class effect.
Impact on the risk-benefit balance of the product	AMS is represented in the risk-benefit balance of all IVIg products. Routine pharmacovigilance activities have been implemented including, but not limited to ongoing signal detection, specific AE questionnaire, and PSUR analysis. These pharmacovigilance activities in addition to the reversibility self-limiting nature of the condition, diagnosis with laboratory tests, and treatment options, supports a favorable risk-benefit balance for IVIg.
Public health impact	No public health impact is anticipated due to standard health care practices.

ADR = adverse drug reaction; AE = adverse event; AMS = aseptic meningitis syndrome; CSF = cerebrospinal fluid; DLP = data lock point; ITP = primary immune thrombocytopenia; IgG = immunoglobulin G; IVIg = intravenous immunoglobulin; SMQ = Standardised Medical Dictionary for Regulatory Activities Query

Important Identified Risk 2: Haemolysis

Important Identified Risk	**Haemolysis** Haemolytic disorders (SMQ) broad
Potential Mechanism	Daw et al (2008) proposed a 2-step mechanism for the development of clinically significant haemolysis after IVIg infusion. The first step is the passive transfer of ABO isohemagglutinins to non-O blood group patients. The second step is the enhanced activity of the immune system in patients with an underlying inflammatory state, with accelerated removal of sensitised red blood cells from the circulation (Daw et al, 2008).
Evidence source	Haemolysis is a known class effect of IVIg products. Cases have been received from multiple sources including case reports from clinical trials, post-marketing, and literature. There have been reported cases with IVIg which provided evidence of a causal association. The evidence sources indicate that haemolysis has an impact on patients in terms of severity / seriousness. Although it is primarily a reversible self-limiting condition, haemolysis is considered an important identified risk for the class of IVIg products.
Characterisation of the risk	Haemolysis is a known class effect of IVIg therapy. It has been shown that this class effect is mainly associated with modern IVIg products manufactured with a purification process that has a very high IgG specificity (Bellac et al, 2015; Daw et al, 2008; Gordon et al, 2009; Kahwaji et al, 2009). A total of 810 post marketing cases (625 for Privigen, 185 for generic IVIg) were identified (DLP of 31 December 2025) and reported a total of 1060855 haemolytic AEs. In addition, there were 14 reports from clinical trials; 12 (frequency 2.5%) from the CIDP clinical trials (IgPro10_3001 and IgPro20_3003), 1 from the ITP PMC study 1 report from the chronic ITP study (ZLB03_003CR). The most frequently reported AEs (> 20) included Haemolysis (340), Haemolytic anaemia (257), Transfusion reaction (93), Coombs direct test positive (62), Anti-erythrocyte antibody positive (48), Autoimmune haemolytic anaemia (31), Delayed haemolytic transfusion reaction (26), Haemoglobinuria (22), and Haptoglobin decreased (21). The majority of AEs describing events of haemolysis were serious (949/1060). Out of the 1060 reported AEs, 905 were assessed by CSL Behring as related, 35 as not related and for 120 AEs causality was not assessable. At the DLP, the outcome for the 1060 reported AEs was as follows: not reported / unknown (452), resolved (411), resolving (98), not resolved (61), fatal (20), resolved with sequelae (14), and resolved with treatment (4). The 20 fatal events included Haemolysis (5), Alloimmune haemolytic anaemia (3), Acute haemolytic transfusion reaction (2), Haemolytic transfusion reaction (2), and 1 each of ABO incompatibility, Autoimmune haemolytic anaemia, Coombs direct test positive, Coombs positive haemolytic anaemia, Haemoglobinuria, Haemolytic anaemia, Haptoglobin decreased, and Intravascular haemolysis; and were reported in 13 cases. All AEs except 1 AE of Haemolysis and the 3 AEs of Alloimmune haemolytic anaemia were assessed by CSL Behring as related. Two cases of haemolysis resulted in acute renal failure. For the majority of cases the temporal relationship was implausible; and / or the patients' comorbid status and other risk factors provided an alternative explanation for death.

CCI [redacted]

Important Identified Risk	**Haemolysis** Haemolytic disorders (SMQ) broad
	These included pregnancy complications, and progression of underlying disease / conditions eg, mantle cell lymphoma, stem cell transplant and cGvHD, myasthenia gravis, myelodysplasia, severe vascular disease, post-operative ischemic complications, and drug induced pneumonitis, and Sickle cell disease. In the DIC cases the patients were suffering from different comorbidities such as acute biphenotypic leukaemia, stem cell transplant, microangiopathy, chronic renal insufficiency, hypertension and / or obesity. In these cases, the doses administered were 240 g and 275 g (1.9 g/kg bw), respectively. In cases of acute renal failure, patients were suffering from different comorbidities including Mantel cell lymphoma, myelodysplasia renal insufficiency, peripheral vascular disease, hyperlipidaemia, hypertension, neuropathy, obesity, cognitive impairment, chronic urinary tract infection. In addition, there were 14 reports from clinical trials: 12 (frequency 2.5%) from the CIDP clinical trials (IgPro10_3001 and IgPro20_3003), 1 from the ITP PMC study 1 report from the chronic ITP study (ZLB03_003CR). None of the haemolysis cases in IVIg clinical studies was complicated with ARF or DIC. The majority of AEs (795/855) describing events of haemolysis were serious. Two of the 14 clinical trial reports were considered serious. All clinical trial cases resolved without the need of blood transfusions. Clinically significant haemolysis associated with IVIg administration is rare (Daw et al, 2008). Mild hemolytic reactions may be of little clinical significance and are outweighed by the benefits of IVIg treatment. A decrease in haemoglobin or a lower than expected increase in hemoglobin after red blood cell transfusion has been reported. Haemolytic reactions may be particularly associated with high-cumulative-dose IVIg therapy (Daw et al, 2008). There seems to be increased reporting of renal failure secondary to haemolysis (Dantal, 2013). There is no known background incidence of haemolysis in the indicated populations. Haemolysis has been reported with administration of high dose IVIg as IVIg can contain blood group antibodies which may act as haemolysins and induce coating of red blood cells with Ig, which can cause haemolysis (Copelan et al, 1986; Misbah et al, 1993; Thomas et al, 1993). The addition of haemolysis to product labelling for IVIg was recommended by the FDA in 2003 (Golding, 2003). In a case study analysis of 1000 patients receiving high dose IVIg, 16 patients (1.6%) showed evidence of haemolysis, with reduced haemoglobin or lower than expected increase in haemoglobin after red blood cell transfusion (Daw et al, 2008). Time to onset was between 12 hours and 10 days after last dose of IVIg. A total of 211 same-day haemolytic reactions were also observed in a retrospective cohort study of 20,440 patients administered subcutaneous or intravenous immunoglobulin products in the US during 2008 to 2014 (Sridhar et al, 2018).

Important Identified Risk	**Haemolysis** Haemolytic disorders (SMQ) broad
Risk factors and risk groups	Non-O blood group patients receiving high dose IVIg are at more risk of haemolysis. The anti-A and anti-B titer of the IVIg product used also appears to play a role, with products with an anti-A titer ≤ 1.16 (measured by direct method according to Ph. Eur.) rarely causing hemolysis (Bellac et al, 2015). Additional potential risk factors for patients developing ARF or DIC as a complication to IVIg-induced hemolysis include medical history of arterial hypertension, diabetes mellitus, age, sucrose (or sucrose-containing) IV preparations, nonhypogamma-globulinemic indications and chronic renal failure. Also patients exposed to drugs modifying the renal hemodynamic such as: ACE-I or ARA, diuretics and nonsteroidal anti-inflammatory drugs (Dickenmann et al, 2008; Lin et al, 2011; Moulis et al, 2011; Onuigbo et al, 2012).
Preventability	Consensus recommendations from the Immunoglobulins in Immunology Expert Group (APIIEG, 2009) recommends that patients with pre-existing hematological disorders who are receiving high dose IVIg should have their hemoglobin levels monitored before, during and after infusion. In a review article, 85% of haemolysis reports received by Health Canada (where dose detail was provided) occurred in patients receiving > 2 g/kg IgG (Taylor et al, 2009). Isoagglutinins are involved in clinically nonsignificant haemolysis after treatment with IVIg but individual susceptibility varies greatly (Mielke et al, 2017). The use of an IVIg product with a low anti-A and / or anti-B titer in patients at risk potentially reduces the risk of hemolysis. Risk minimisation measures for the reduction of isoagglutinins in IVIg have been implemented and completed: Until 2013, the Privigen production process did not contain an isoagglutinin reduction step. Anti-A / B isoagglutinin titres were therefore higher in Privigen than in some other IVIg products (median anti-A 1:32, median anti-B 1: 16, all measured by the direct haemagglutination test method according to Ph. Eur.) From Q3 2013, Privigen was produced mainly from anti-A isoagglutinin screened plasma, ie, plasma from which approximately 5% of donors with high anti-A titres were excluded (median anti-A 1:32, median anti-B 1: 16, all measured by the direct haemagglutination test method according to Ph. Eur.). The implementation of this donor screening was followed by a reduction of the incidence of haemolytic events (refer to PASS [IgPro10_5003] Interim Report 2 and INC Privigen Hemolysis Reduction Poster [Shebl et al, 2016]) (Martinez et al, 2018). From Q4 2015 onwards, the production of Privigen and Hizentra® has included a specific IAC step, resulting in median anti-A 1:8 and median anti-B 1:4 as measured by the direct haemagglutination test method. This step is being implemented at different time points in different countries as regulatory approval is obtained. An 89% reduction in the incidence rate of hemolytic anemia was observed following the implementation of the IAC step compared to the incidence rate from 2008 to 2012 prior to the implementation of donor screening or IAC (refer to PASS [IgPro10_5003] Final Report of Study Result). The IAC step resulted in substantial

Important Identified Risk	**Haemolysis** Haemolytic disorders (SMQ) broad
	reductions of spontaneous reports of haemolysis worldwide (Shebl et al, 2018, Shebl et al, 2019).
Impact on the risk-benefit balance of the product	Haemolysis is represented in the risk-benefit balance of all IVIg products. Routine pharmacovigilance activities have been implemented including, but not limited to ongoing signal detection, specific AE questionnaire, and periodic aggregate analysis. Furthermore, additional risk minimisation measures for haemolysis were introduced (Donor screening and IAC step in manufacturing). These pharmacovigilance activities and risk minimisation measures in addition to the rarity and reversibility nature of this reaction revealed a favorable risk-benefit balance for IVIg.
Public health impact	No public health impact is anticipated due to risk minimisation measures for haemolysis and standard health care practices.

ACE = angiotensin converting enzyme; AE = adverse event; ARA = angiotensin receptor antagonists; ARF = acute renal failure; CIDP = chronic inflammatory demyelinating polyneuropathy; cGvHD = chronic graft versus host disease; DIC = disseminated intravascular coagulopathy; DLP = data lock point; FDA = Food and Drug Administration; IAC = immunoaffinity chromatography; Ig = immunoglobulin; IgG = immunoglobulin G; INC = Inflammatory Neuropathy Consortium; ITP = primary immune thrombocytopenia; IV = intravenous; IVIg = intravenous immunoglobulin; PASS = post-authorisation safety study; Ph. Eur. = European Pharmacopoeia; PMC = post-marketing commitment; SMQ = Standardised Medical Dictionary for Regulatory Activities Query; US = United States

Important Identified Risk 3: Hypersensitivity and anaphylactic reactions

Important Identified Risk	**Hypersensitivity and anaphylactic reactions** Anaphylactic reactions (SMQ) narrow and Hypersensitivity (SMQ) narrow
Potential Mechanism	The exact mechanism through which hypersensitivity reactions occur is often unclear and varies among drugs (Lenz, 2007), however, drug allergic reactions can be immune mediated or pseudoallergic (Warrington and Silviu-Dan, 2011). The Gell and Coombs' classification system distinguishes immune mediated allergic reactions as immediate (mediated by IgE antibodies), cytotoxic or immune complex reactions (both mediated by IgG or IgM antibodies), and delayed type reactions (mediated by cellular immune mechanisms such as T cell activation) (Mirakian et al, 2009; Warrington and Silviu-Dan, 2011). To be immunogenic, drugs may act as haptens or prohaptens or may directly interact with T cell receptors to elicit an immune response (Schnyder and Pichler, 2009). Pseudoallergic reactions are not associated with the production of antibodies or sensitised T cells, but are thought to result when the drug is able to directly stimulate release of inflammatory mediators such as histamine, prostaglandins, leukotrienes or kinins (Warrington and Silviu-Dan, 2011).
Evidence source	Hypersensitivity and anaphylactic reactions are known class effect of IVIg products. Cases have been received from multiple sources including case reports from clinical trials, post-marketing, and literature. There have been

Important Identified Risk	**Hypersensitivity and anaphylactic reactions** Anaphylactic reactions (SMQ) narrow and Hypersensitivity (SMQ) narrow
	reported cases with IVIg which provided evidence of a causal association. The evidence sources indicate that hypersensitivity and anaphylactic reactions have impact on patients in terms of severity / seriousness. Hypersensitivity and anaphylactic reactions are considered an important identified risk for plasma-driven products including the class of IVIg products.
Characterisation of the risk	A total of 3882 post marketing cases (3535 for Privigen, 347 for generic IVIg) describing hypersensitivity were identified (to DLP of 31 December 2025) reporting 5167 hypersensitivity and / or anaphylactic reactions. The most frequently reported AEs (> 30) were Rash (1165), Hypersensitivity (751), Urticaria (705), Anaphylactic reaction (304), Infusion related reaction (322), Drug hypersensitivity (210), Rash pruritic (173), Eczema (158), Rash erythematous (108), Rash maculo-papular (81), Swelling face (73), Bronchospasm (73), Dermatitis allergic (65), Angioedema (66), Anaphylactic shock (55), Rash macular (56), Swollen tongue (37), Rash papular (35), Circulatory collapse (32), and Anaphylactoid reaction (34). The majority (3067/5167) of AEs related to hypersensitivity and / or anaphylactic reactions were nonserious. Out of the 5167 reported AEs, 4266 were assessed by CSL Behring as related, 221 as not related and for 680 AEs causality was not assessable. At the DLP of this report, the outcome for the 5167 reported AEs was as follows: resolved (2471), not reported / unknown (1843), resolving (406), not resolved (371), resolved with treatment (28), resolved with sequelae (27), and fatal (21). The 21 fatal events included Circulatory collapse and Shock (4 each), Alloimmune haemolytic anaemia (3), Anaphylactic reaction and Anaphylactic shock (2 each), and Urticaria, Toxic epidermal necrolysis, Rash, Bronchospasm, Hypersensitivity, and Drug hypersensitivity (1 each); and were reported in 19 cases. Out of these 21 fatal events, 9 events including Circulatory collapse (3), Alloimmune haemolytic anaemia (3), Shock (2), and Anaphylactic shock (1) were assessed by CSL Behring as not related and more plausibly explained by the patient's multiple comorbidities including renal failure, arterial hypertension, hepatic steatosis, myelodysplastic syndrome, increased fragility of vessels and diverticulitis, myocardial failure, recurrent pneumonia, pregnancy complications, fulminant GBS and cardiac decompensation, and coadministered products;. The remaining 11 events were assessed as related predominantly due to close termporal relationship. However, the underlying conditions such as immunodeficiency, toxic epidermal necrolysis, suspected toxic shock syndrome, worsening multiorgan failure, infection and septicaemia were considered as possible confounders. Additionally, there have been 6 reports of hypersensitivity (1.2%) and no anaphylactic reactions reported in clinical trials. Common symptoms include acute urticaria; prompt initial treatment is essential as delay can lead to hypoxic-ischemic encephalopathy or death (Simons et al, 2013). In a 10-year retrospective study, shock was documented in 41% of 294 patients with anaphylaxis, which occurred typically in elderly patients with initial symptoms of syncope, dizziness, and cyanosis after exposure to radiocontrast media or drugs (Simons et al,

Important Identified Risk	**Hypersensitivity and anaphylactic reactions** Anaphylactic reactions (SMQ) narrow and Hypersensitivity (SMQ) narrow
	2013). In infants and children with anaphylaxis, hypotension is an uncommon initial manifestation, typically only occurring in severe episodes (Simons et al, 2013). In 1 Spanish study, mucocutaneous and lower respiratory signs or symptoms were the most frequent clinical findings (Moro et al, 2011). In general, drug allergies are associated with a variety of different symptoms including exanthemata, acute urticaria, anaphylaxis and toxic epidermal necrolysis. Allergies often lead to drug discontinuation, and some clinical manifestations (eg, anaphylaxis and toxic epidermal necrolysis) may prove fatal (Warrington and Silviu-Dan, 2011). Allergic / hypersensitivity / anaphylactic reactions are a known class effect of Igs and have been observed in patients treated with IVIg regardless of product (Gardulf, 2007; Horn et al, 2007; Misbah et al, 1993; Quinti et al, 2008; Reisman et al, 2009). Sensitisation (IgE antibodies) to foreign proteins in the environment is present in up to 40% of the population worldwide and ADRs may affect up to 10% of the world's population (WHO White Book on Allergy, 2012). The standardised cumulative incidence of anaphylaxis, as measured by episodes of anaphylaxis per 1000 hospital emergency admissions, according to the Standardised European Population was 1.1 per 1000 admissions (95% CI, 0.9 to 1.2). Age distribution using the number of emergencies via logistic regression showed that the patients aged 5 to 9 years (OR, 0.3), 20 to 29 years (OR, 0.4), 30 to 39 years (OR, 0.5), and > 69 years (OR, 0.3) had a lower risk of attending the emergency department due to anaphylaxis than the reference age group (0 to 4 years) (Moro et al, 2011). For the indicated patients no specific incidence / prevalence is available, however it is considered to be no different to the general population.
Risk factors and risk groups	IVIg may present an increased risk of anaphylaxis in IgA deficient patients as it contains traces of IgA. Although the role of IgA in anaphylactic reactions is controversial (Sandler et al, 2015). It is not anticipated that the risk of allergic / hypersensitivity / anaphylactic reactions be any different to other IVIg products. Privigen has a low IgA content (≤ 0.025 mg/mL), compared to most other IVIg products. General factors that increase the likelihood of Type 1 hypersensitivity include repeated exposure to the drug and a history of hypersensitivity to a drug of the same chemical class (Lenz, 2007).
Preventability	The contraindications section of the PI states that the product is contraindicated in patients who have: • A history of anaphylactic or severe systemic reaction to the administration of human Ig. • IgA deficiency with antibodies to IgA and a history of hypersensitivity. Although it is rare, human normal Ig can induce anaphylactic reaction, even in patients who had tolerated previous treatment with human normal Ig.
Impact on the risk-benefit balance of the product	Hypersensitivity and anaphylactic reactions are represented in the risk-benefit balance of all IVIg products. Routine pharmacovigilance activities have been implemented including, but not limited to ongoing signal

Important Identified Risk	**Hypersensitivity and anaphylactic reactions** Anaphylactic reactions (SMQ) narrow and Hypersensitivity (SMQ) narrow
	detection, specific AE questionnaire, and periodic aggregate analysis. These pharmacovigilance activities and nature of these reactions indicated a favorable risk-benefit balance for IVIg.
Public health impact	No public health impact is anticipated due to standard health care practices.

ADR = adverse drug reaction; AE = adverse event; CI = confidence interval; DLP = data lock point; GBS = Guillain-Barré syndrome; IgA/E/G/M = immunoglobulin A/E/G/M; IVIg = intravenous immunoglobulin; OR = odds ratio; PI = Product information; SMQ = Standardised Medical Dictionary for Regulatory Activities Query

Important Identified Risk 4: Thromboembolic events

Important Identified Risk	**Thromboembolic events** Embolic and thrombotic events (SMQ); includes sub-SMQs Embolic and thrombotic events, arterial (SMQ); Embolic and thrombotic events, venous (SMQ); Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ).
Potential Mechanism	A potential cause of TEEs due to IVIg is the demonstrable increase in viscosity, which increases in a linear fashion as a function of the increased IgG level (Brown and Ballas, 2003). Although small increases in serum viscosity affect capillary blood flow and could promote aggregation of Ig, they are inconsequential in healthy people. However, in patients with pre-existing high-normal serum viscosity (from hypergammaglobulinemia, hyperfibrinogenemia or hypercholesterolemia), who have other risk factors such as impaired cardiac output, carotid artery disease, hypercoagulable status, immune complex formation, leukocytosis or thrombocytosis, even minor increases in viscosity may tip the rheology balance and cross the symptomatic viscosity threshold precipitating TEEs (Dalakas and Clark, 2003). For some IVIg products, the presence of FXIa has been postulated to play a significant role in TEEs. However, the Privigen production process was been shown to remove this thrombogenic factor (Komenda et al, 2014).
Evidence source	TEEs are known class effect of IVIg products. Cases have been received from multiple sources including cases from clinical trials, post marketing, and literature. There have been reported cases with IVIg which provided evidence of a causal association. The evidence sources indicate that TEEs have impact on patients in terms of severity / seriousness. Although these events primarily occur in patients with underlying risk factors, TEEs are considered an important identified risk for the class of IVIg products.
Characterisation of the risk	A total of 676 post marketing cases (499 for Privigen, 177 for generic IVIg) were identified (DLP of 31 December 2025) reporting 864 TEEs. The most frequently reported AEs (> 20) were Pulmonary embolism (171), Deep vein thrombosis (90), Thrombosis (67), Cerebrovascular accident (63), Myocardial infarction (48), Acute myocardial infarction (32),

Important Identified Risk	**Thromboembolic events** Embolic and thrombotic events (SMQ); includes sub-SMQs Embolic and thrombotic events, arterial (SMQ); Embolic and thrombotic events, venous (SMQ); Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ).
	Transient ischaemic attack (26), and Ischaemic stroke (23) and Superficial vein thrombosis (22). The majority (837/864) of reported TEEs were serious. Out of the 864 reported AEs, 558 were assessed by CSL Behring as related, 96 as not related and for 210 AEs causality was not assessable. At the DLP, the outcome for the 864 reported AEs was as follows: not reported / unknown (389), resolved (192), resolving (95), not resolved (87), fatal (68), resolved with sequelae (29), and resolved with treatment (4). Of the 68 fatal AEs, the most frequently reported AEs (≥ 2) were Myocardial infarction (12), Pulmonary embolism (10), Cerebrovascular accident (7), Deep vein thrombosis and Haemorrhagic stroke (4 each), Acute myocardial infarction, Infarction, Amaurosis fugax , thrombosis, Embolic stroke, Ischaemic cerebral infarction, and Ischaemic stroke (2 each).; all were reported in 54 cases. In the vast majority, patients had confounding medical histories and / or risk factors that may provide alternative etiologies for event onset. These included; autoimmune hepatitis, atrial fibrillation, hypertension, atrial fibrillation, and cardiovascular disease , Type II diabetes, malignancy, history of smoking, advanced age, chronic renal failure, obesity, steroid therapy, COVID-19, GBS, arterial hypertension, graft versus host disease, haemolysis and immunodeficiency. An additional 2 serious reports (0.4%) with underlying risk factors for thromboembolism were reported in the clinical trials. No deaths were reported from clinical trials. TEEs in patients at high risk for vascular disease are a frequent side effect of IVIg therapy (Dalakas and Clark, 2003). Although TEEs are rare, they may have disabling or catastrophic consequences (Dalakas and Clark, 2003). Strokes can occur at any time during the long-term administration of IVIg (Dalakas and Clark, 2003). The annual incidence of venous thrombosis in the general population increases dramatically with age, and is estimated to be between 1 per 10,000 person-years in childhood to 1% in the elderly (Fowkes et al, 2003; Isma et al, 2009; Rosendaal, 1999). Recent estimates in general EU and North American populations estimate the incidence of venous TEEs between 90 to 201 per 100,000 person-years (Alotaibi et al, 2016; Arshad et al, 2017). For arterial TEEs, incidence of myocardial infarction has been estimated between 80 to 207 per 100,000 person-years and ischemic stroke between 63 to 140 per 100,000 person-years in European and North American general populations (IHME, 2019; Roger et al, 2010). GBD 2017 Results Tool (GBD 2017 Collaborators; Widimsky et al, 2010). For the proposed indications, no specific incidence / prevalence was available.

Important Identified Risk	**Thromboembolic events** Embolic and thrombotic events (SMQ); includes sub-SMQs Embolic and thrombotic events, arterial (SMQ); Embolic and thrombotic events, venous (SMQ); Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ).
Risk factors and risk groups	It has been suggested that older patients, patients with low cardiac output, and patients with atherosclerotic disease are at higher risk of side effects from increased serum viscosity (Brown and Ballas, 2003). However, TEEs are believed to be rare in antibody-deficient patients receiving IVIg at replacement doses (200 to 600 mg/kg), as the increase in serum viscosity at such doses is minimal (Brown and Ballas, 2003). Patients with vascular risk factors or known vascular disease who require IVIg may be at an increased risk of development of thromboembolic phenomena, regardless of dose or autoimmune disease (Brown and Ballas, 2003). IVIg-treated neurologic patients may be more prone to strokes, as their long-standing muscle weakness, impaired mobility or wheelchair confinement could facilitate a subclinical hypercoagulable state or formation of silent clots, especially in patients at high risk for vascular disease (Dalakas and Clark, 2003).
Preventability	The predictability and preventability of TEEs is not known. However patients at risk include those with a history of atherosclerosis, multiple cardiovascular risk factors, advanced age, impaired cardiac output, coagulation disorders, prolonged periods of immobilisation, and / or known / suspected hyperviscosity. Slowing the rate of infusion and avoidance of concomitant use of other blood products may reduce the risk of TEEs, particularly in patients administered high doses.
Impact on the risk-benefit balance of the product	TEEs are represented in the risk-benefit balance of all IVIg products. Routine pharmacovigilance activities have been implemented including, but not limited to, ongoing signal detection, specific AE questionnaire, and periodic aggregate analysis. These pharmacovigilance activities indicate a favorable risk-benefit balance for IVIg.
Public health impact	No public health impact is anticipated due to standard health care practices.

AE = adverse event; DLP = data lock point; EU = European Union; FXIa = activated factor XI; GBD = Global Burden of Disease; GBS = GBS = Guillain-Barré syndrome; IgG = immunoglobulin G; IVIg = intravenous immunoglobulin; SMQ = Standardised Medical Dictionary for Regulatory Activities Query;
TEE = thromboembolic events

Important Identified Risk 5: Acute renal failure

Important Identified Risk	**Acute renal failure** Acute renal failure (SMQ) narrow
Potential Mechanism	Sucrose (and to a lesser extend maltose and glucose), used as a stabilizer in some IVIg products, can cause osmotic nephrosis. Privigen uses L-proline as a stabilizer, which does not have a direct impact on the kidneys. Acute hemolysis and secondary ARF have been reported following sucrose-free IVIg infusion. There seems to be increased reporting of renal failure secondary to hemolysis caused by some amino acid-stabilized IVIg products (Dantal, 2013).
Evidence source	ARF is a known class effect of IVIg products. Cases have been received from multiple sources including cases from clinical trials, postmarketing, and literature. There have been reported cases with IVIg which provided evidence of a causal association. The evidence sources indicate that ARF has impact on patients in terms of severity / seriousness. ARF is considered an important identified risk for the class of IVIg products, especially sugar-containing IVIg.
Characterisation of the risk	A total of 196 post marketing cases (152 for Privigen, 44 for generic IVIg) were identified (DLP of 31 December 2025) reporting 218 AEs relevant to ARF, as follows: Acute kidney injury (86), Renal failure (63), Renal impairment (39), Anuria (10), Nephropathy toxic (8), Dialysis (6), Oliguria (4), and 1 each of Azotaemia and Prerenal failure. The majority (217/218) of AEs related to ARF were serious. Out of the 218 reported AEs, 135 were assessed by CSL Behring as related, 43 as not related and for 40 AEs causality was not assessable. At the DLP, the outcome for the 218 reported AEs was as follows: not reported / unknown (94), resolved (52), fatal (30), not resolved (25), resolving (13), resolved with sequelae (3), and resolved with treatment (1). The 30 fatal AEs included Renal failure (15), Acute kidney injury (12), Renal impairment (2) and Dialysis (1) were reported in 27 cases. In the vast majority of the cases, the patients had underlying conditions (and comorbidities) or cosuspect drugs which provide alternative explanations for the deaths. These included; renal transplants, chronic renal failure, chronic renal insufficiency, CLL, multiple myeloma, lymphoma, mantel cell lymphoma, sepsis, type II diabetes, arterial hypertension, plasmocytoma, pneumogenic sepsis and immunodeficiency. Two patients experienced ARF as a complication of hemolysis. Additionally, 2 cases (0.2%) were reported from clinical trials. No deaths were reported from clinical trials. ADRs involving the kidney with sucrose-free IVIg products are relatively rare but serious events (Dantal, 2013). A recent review of IVIg therapy and acute kidney disease (using the DrugCite database; www.drugcite.com) found the following renal impairment-associated AEs for the period 2007 to 2011: anuria, hemodialysis, renal failure, renal failure chronic, and kidney transplant rejection. Although the incidence of ARF is low, the consequences can be severe (Dantal, 2013). Renal dysfunction / failure may accompany many different diseases; therefore it is difficult to ascertain a background incidence in the general population. There is no reported background incidence of renal dysfunction in patients with PID. Some types of PID (eg, CVID, selective

Important Identified Risk	**Acute renal failure** Acute renal failure (SMQ) narrow
	IgA, and particularly, complement deficiencies) may be associated with autoimmune diseases such as systemic lupus erythematosis which can affect all organs of the body including the kidneys (Arason et al, 2010), therefore the incidence may be slightly higher in these patient groups than the healthy population. Renal dysfunction / failure was considered to be related to the addition of sucrose as a stabilizer in some IVIg products during the 1980's. In a US Centers for Disease Control and Prevention report (2007), 90% of the 120 cases of acute renal failure had been treated with sucrose-stabilized IVIg products (Caress et al, 2010), and less than 5% were in patients with PID despite approximately 25% of IVIg use being for this indication in the US (Pierce and Jain, 2003).
Risk factors and risk groups	Due to the use of L-proline as a stabilizer in Privigen, the risk of renal dysfunction / failure is anticipated to be small. IVIg associated- renal failure mostly occurs in patients with pre-existing conditions or those at increased risk of renal ADRs, such as patients with prior renal insufficiency, diabetes mellitus, advanced age (> 65 years of age), dehydration or hypervolemia, sepsis, paraproteinemia or those concomitantly using other agents known to cause renal toxicity (Dantal, 2013).
Preventability	As discussed above, most of the cases of renal failure are associated with sucrose-containing IVIg products. Privigen contains L-proline as stabilizer, which is reported to be kidney protective (Singer et al, 2001). Appropriate wording exists in the PI that patients at risk (pre-existing renal insufficiency, diabetes mellitus, hypovolaemia, sepsis, paraproteinemia, overweight, concomitant nephrotoxic medicinal products or age > 65) should be administered IVIg at the minimum dose and infusion rate practicable.
Impact on the risk-benefit balance of the product	ARF is represented in the risk-benefit balance of all IVIg products. Routine pharmacovigilance activities have been implemented including, but not limited to ongoing signal detection, specific AE questionnaire, and periodic aggregate analysis. These pharmacovigilance activities including monitoring of patients with risk factors such as pre-existing renal disease and / or concomitant nephrotoxic medications indicated a favorable risk-benefit balance for IVIg.
Public health impact	No public health impact is anticipated due to standard health care practices.

ADR = adverse drug reaction; AE = adverse event; ARF = acute renal failure; CLL = chronic lymphocytic leukaemia; CVID = common variable immunodeficiency; DLP = data lock point; IgA = immunoglobulin A; IVIg = intravenous immunoglobulin; PI = Product information; PID = primary immunodeficiency; SMQ = Standardised Medical Dictionary for Regulatory Activities Query; US = United States

Important Potential Risk 1: Transfusion-related acute lung injury

Important Identified Risk	**Transfusion-related acute lung injury** MedDRA PTs: Transfusion-related acute lung injury and Acute lung injury
Potential Mechanism	The current view is that the cause of TRALI is the transfer of anti- HLA antibodies from the donor to the recipient. A diagnosis of TRALI is strongly supported if anti-HLA antibodies or other anti-leucocyte antibodies are identified in the donor's plasma (Collins et al, 2014). IVIg has the capacity to cause TRALI if it contains significant of antileukocyte antibodies directed against antigens on the host leukocytes (Silliman et al, 2005). A 2-hit model of pathogenesis has been proposed to explain the development of TRALI. The first hit is underlying patient risk factors, resulting in adherence of primed neutrophils to the pulmonary endothelium. The second hit is caused by mediators in the blood transfusion (includes any blood products eg, red blood cells, plasma, platelets) that activate the endothelial cells and pulmonary neutrophils leading to capillary leakage and subsequent pulmonary edema (Vlaar and Juffermans, 2013).
Evidence source	TRALI is a known class effect of blood / plasma-driven transfusions. Cases have been received from multiple sources including post-marketing, and literature. There have been reported cases with IVIg which provided no evidence of a causal association due to multiple confounding factors. The evidence sources indicate that TRALI has an impact on patients in terms of severity / seriousness. TRALI is considered an important potential risk for IVIg due to the rarely reported cases and the presence of multiple confounding factors.
Characterisation of the risk	A total of 54 post marketing cases (39 for Privigen, 15 for generic IVIg) were identified (DLP of 31 December 2025) reporting 54 events of Transfusion-related acute lung injury and 1 event of Acute lung injury. All 55 AEs were serious. Out of the 55 reported AEs, 48 were assessed by CSL Behring as related, 4 as not related and for 3 AEs causality was not assessable. At the DLP of this report, the outcome for the 44 reported AEs was as follows: resolved (21), not reported / unknown (16), resolving (6), not resolved (6), fatal (5), and resolved with sequelae (1). The 5 fatal AEs of Transfusion-related acute lung injury were reported in 5 cases and 3 were assessed as related. One was assessed as not related, and the remaining 1 was unassessable. In a number of cases there were alternative explanations (eg., lung transplant rejection, anaphylactic reaction, underlying pulmonary or cardiac disease, SLE, asthma, immunodeficiency, myelodysplastic syndrome, complicated post-bone marrow course with CMV reactivation and renal insufficiency) or confounders (eg., cosuspect drugs including blood transfusions, fludarabine, phenylephrine). No cases were reported in clinical trials. TRALI is a serious life threatening complication of blood component therapy (Silliman et al, 2005). TRALI typically presents within 1 to 6 hours after infusion, as a clinical syndrome characterised by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, no pre-existing acute lung injury before transfusion and fever.

Important Identified Risk	**Transfusion-related acute lung injury** MedDRA PTs: Transfusion-related acute lung injury and Acute lung injury
	TRALI is a clinical diagnosis of exclusion and no diagnostic tests are available. The incidence of TRALI is estimated to be between 0.08 and 15% of patients receiving a blood transfusion. The large variation in estimates of TRALI may be explained by the following factors: diversity in clinical symptoms, absence of specific disease markers and diagnostic tests, and the absence of a clear definition (Vlaar and Juffermans, 2013).
Risk factors and risk groups	The incidence of TRALI is 50 to 100 times higher in critically ill patients than in the general population. Patients suffering from a clinical disorder such as sepsis are increasingly recognised as being at risk for development of TRALI (Vlaar and Juffermans, 2013).
Preventability	Two groups of high risk donors have been identified: multiparous female donors and donors previously exposed to blood transfusion. Mitigation strategies include exclusion of donors (the FDA recommendation: adopt a mainly male donor strategy) and pooling of plasma (leading to the dilution of any leucocyte antibodies present [Vlaar and Juffermans, 2013]).
Impact on the risk-benefit balance of the product	Routine pharmacovigilance activities have been implemented including, but not limited to ongoing signal detection, specific AE questionnaire, and periodic aggregate analysis. These pharmacovigilance activities including monitoring of patients with risk factors such as underlying concomitant conditions indicated a favorable risk-benefit balance for IVIg.
Public health impact	No public health impact is anticipated due to standard health care practices.

AE = adverse event; CMV = cytomegalovirus; DLP = data lock point; FDA = Food and Drug Administration; HLA = human leukocyte antigen; IVIg = intravenous immunoglobulin; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SLE = systemic lupus erythematosus; TRALI = transfusion-related acute lung injury

Important Potential Risk 2: Potential for transmission of infectious agents

Important Identified Risk	**Potential for transmission of infectious agents** MedDRA High Level Group Term: Viral infectious disorders; High Level Terms: Infectious transmissions, Virus identification and serology. MedDRA PTs: Hepatitis post transfusion, Viraemia, Viral sepsis.
Potential Mechanism	The likelihood of transmitting infectious agents with IVIg is very low, due to the steps undertaken during the manufacturing and processing of the product.
Evidence source	The potential for transmitting infectious agents is a known class effect of all blood / plasma-driven products. Cases have been received from multiple sources including post-marketing, and literature. There have been reported cases with IVIg; none of them provided evidence of confirmed cases of transmission of infectious agents. For these reasons, potential for

Important Identified Risk	**Potential for transmission of infectious agents** MedDRA High Level Group Term: Viral infectious disorders; High Level Terms: Infectious transmissions, Virus identification and serology. MedDRA PTs: Hepatitis post transfusion, Viraemia, Viral sepsis.
	transmission of infectious agents is considered an important potential risk for IVIg. The evidence sources indicate that the potential for transmission of infectious agents has an impact on patients in terms of severity / seriousness. Potential for transmission of infectious agents is considered an important potential risk for the IVIg class of products.
Characterisation of the risk	There are no confirmed cases of transmission of infectious agents reported with IVIg from clinical trials or post-marketing experience. Review of the published literature revealed 2 articles describing the transmission of HCV in patients treated with IVIg before the introduction of effective virus elimination measures. In the first study, 23 (11%) of 341 patients receiving IVIg treatment became infected with HCV (Bresee et al, 1996). In the second study, a survey of patients treated with IVIg in the US identified 58 cases of HCV. Of these 58 patients, 37 were treated for common variable immune deficiency, 9 for X-lined agammaglobulinemia, 5 were IgG subclass deficient, 4 were antibody deficient with normal Ig levels, 2 had severe combined immunodeficiency after blood and marrow transplant and 1 had B cell linker deficiency (Razvi et al, 2001). None of the IVIg treatments currently available (all MAHs) in the EU has ever transmitted HCV. The transmission of infectious agents has the potential for serious long-term effects on the individual, in terms of morbidity and mortality. Depending on the infectious agent transmitted, the impact on the patient has the potential to be mild and self-limiting or serious, chronic, and life- threatening. The incidence / prevalence of infectious agents such as HIV, HCV and HBV in patients with primary and secondary immunodeficiency, ITP, GBS, Kawasaki disease, and CIDP is unknown.
Risk factors and risk groups	All patients treated with IVIg, although the risk is very low.
Preventability	The risk of transmission of infectious agents is minimised for the currently known viruses considered to be transfusion relevant, by standard measures including careful donor selection and extensive testing of donations. Validation studies and investigations utilising relevant viruses have demonstrated that the manufacturing procedures are effective in reducing these viruses. The production process of Privigen includes pathogen reduction steps, representing 3 different mechanisms, namely virus inactivation, filtration and partitioning. Enveloped viruses, as well as the nonenveloped parvovirus B19, are effectively inactivated during low pH incubation.
Impact on the risk-benefit balance of the product	Routine pharmacovigilance activities have been implemented including, but not limited to ongoing signal detection, specific AE questionnaire, and periodic aggregate analysis. These pharmacovigilance activities including monitoring of patients with suspicion of the transmission of infectious agents indicated a favourable risk-benefit balance for IVIg.
Public health impact	Of significant potential concern, although the risk is very low. Transmission of identified / known viruses is unlikely.

CCI [redacted]

AE = adverse event; CIDP = chronic inflammatory demyelinating polyneuropathy; EU = European Union; GBS = Guillain-Barré syndrome; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ITP = primary immune thrombocytopenia; IVIg = intravenous immunoglobulin; MAH = marketing authorisation holder; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term

SVII.3.2 Presentation of the missing information

Missing information 1: Neurotoxicity of L-proline in the paediatric population when used at high dose

Evidence source:

Some published studies have shown that long-term treatment with high doses of L-proline has an effect on brain development in very young rats. However, in studies where the dosing was designed to reflect the clinical indications for Privigen, no effects on brain development were observed.

Anticipated risk / consequence of the missing information:

Case reports of paediatric patients receiving high dose ie, for Kawasaki disease are evaluated on a monthly basis since Privigen first launch in 2008 until now (ongoing) for any adverse drug reactions under the Medical Dictionary for Regulatory Activities System Organ Class 'Nervous system disorders'. No cases were confirmed to provide evidence of a causal relationship of neurotoxicity due to L-Proline in association with the use of high dose of Privigen. CSLB is continuing monitoring of any potential cases in the context of this missing information.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII-1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Aseptic meningitis syndrome • Haemolysis • Hypersensitivity and anaphylactic reactions • Thromboembolic events • Acute renal failure
Important potential risks	• Transfusion-related acute lung injury • Potential for transmission of infectious agents
Missing information	• Neurotoxicity of L-proline in the paediatric population when used at high dose

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities include the following; specific adverse event questionnaires, ongoing signal detection, and Periodic Safety Update Report analysis.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires for the important identified risks:**
  - Aseptic Meningitis Syndrome (AMS) for Immunoglobulin Products: specific follow-up questionnaire
  - Haemolysis with Immunoglobulins: specific follow-up questionnaire
  - Allergic / Anaphylactic Reactions for all Products: follow-up questionnaire
  - Thromboembolic Events (TEE): specific follow-up questionnaire
  - Acute Renal Failure (ARF) after Immunoglobulin (IG) Therapy: specific follow-up questionnaire

- **Specific adverse reaction follow-up questionnaires for the important potential risks:**
  - Transfusion-Related Acute Lung Injury (TRALI): specific follow-up questionnaire
  - Transmission of Infectious Agents: specific follow-up questionnaire
- **Other forms of routine pharmacovigilance activities for safety concerns:**

Not applicable

III.2 Additional pharmacovigilance activities

There are no ongoing or planned additional pharmacovigilance activities which are required to address safety concerns or to measure the effectiveness of risk minimisation measures.

III.3 Summary table of additional pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

No post-authorisation efficacy studies are ongoing or planned.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1 Routine risk minimisation measures

Table Part V.1-1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Aseptic meningitis syndrome	Routine risk communication: • SmPC section 4.4 Special warning and precautions for use • SmPC section 4.8 Undesirable effects
Hemolysis	Routine risk communication: • SmPC section 4.4 Special warning and precautions for use • SmPC section 4.8 Undesirable effect
Hypersensitivity and anaphylactic reactions	Routine risk communication: • SmPC section 4.4. Special warning and precautions for use • SmPC section 4.8 Undesirable effect
Thromboembolic events	Routine risk communication: • SmPC section 4.4. Special warning and precautions for use • SmPC section 4.8 Undesirable effects
Acute renal failure	Routine risk communication: • SmPC section 4.4. Special warning and precautions for use • SmPC section 4.8 Undesirable effects
Transfusion-related acute lung injury	Routine risk communication: • SmPC section 4.4. Special warning and precautions for use • SmPC section 4.8 Undesirable effects
Potential for transmission of infectious agents	Routine risk communication: • SmPC section 4.4 Special warning and precautions for use
Missing information: Neurotoxicity of L-proline in the paediatric population when used at high dose	None

SmPC = Summary of Product Characteristics

V.2 Additional risk minimisation measures

There are no current additional risk minimisation measures. Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V.3-2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Aseptic meningitis syndrome	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: None
Hemolysis	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: None
Hypersensitivity and anaphylactic reactions	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: None
Thromboembolic events	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: None
Acute renal failure	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Transfusion-related acute lung injury	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: None
Potential for transmission of infectious agents	Routine risk minimisation measures: SmPC section 4.4 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Follow-up questionnaire Additional pharmacovigilance activities: None
Missing information: Neurotoxicity of L-proline in the paediatric population when used at high dose	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

SmPC = Summary of Product Characteristics

Part VI: Summary of the risk management plan

Summary of risk management plan for Privigen (human normal immunoglobulin for intravenous administration)

This is a summary of the RMP for Privigen. The RMP details important risks of Privigen how these risks can be minimised, and how more information will be obtained about Privigen's risks and uncertainties (missing information).

Privigen's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Privigen should be used.

This summary of the RMP for Privigen should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report.

Important new concerns or changes to the current ones will be included in updates of Privigen's RMP.

I. The medicine and what it is used for

Privigen is used for replacement therapy in adults, and children and adolescents in immunodeficiency syndromes and hypogammaglobulinaemia of specified reasons; for immunomodulation in adults, and children and adolescents in ITP, GBS, Kawasaki disease and CIDP, and MMN; and for prevention of measles in susceptible adults, children and adolescents who are unable to receive measles immunisation (see SmPC for the full indication). It contains human normal immunoglobulin 10% solution for IV administration as the active substance and it is given by infusion.

Further information about the evaluation of Privigen's benefits can be found in Privigen's European Public Assessment Report, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage: Privigen EPAR.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Privigen, together with measures to minimise such risks and the proposed studies for learning more about Privigen's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Privigen is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Privigen are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Privigen. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Aseptic meningitis syndrome • Hemolysis • Hypersensitivity and anaphylactic reactions • Thromboembolic events • Acute renal failure

List of important risks and missing information	
Important potential risks	• Transfusion-related acute lung injury • Potential for transmission of infectious agents
Missing information	• Neurotoxicity of L-proline in the paediatric population when used at high dose

II.B Summary of important risks

Important Identified Risk 1: Aseptic meningitis syndrome	
Evidence for linking the risk to the medicine	Clinical and post-marketing experience.
Risk factors and risk groups	Risk factors for the onset of aseptic meningitis syndrome include the following: • Children with autoimmune diseases appear to be predisposed to developing aseptic meningitis syndrome following IVIg therapy (Caress et al, 2010). • The vast majority of children who develop aseptic meningitis syndrome following IVIg are treated for ITP (Hamrock, 2006). • Rapid infusion rate (AAAAI, 2010; Hopkins and Jolles, 2005) • Repeated IVIg infusion (AAAAI, 2010) • History of headache and migraine (Hamrock, 2006; Hopkins and Jolles, 2005; Scribner et al, 1994; Sekul et al, 1994) • In persons with community-acquired meningitis, aseptic meningitis is significantly more common than bacterial meningitis; 96% of children with CSF pleocytosis have aseptic meningitis (Bamberger et al, 2010). • Seasonality is important in predicting the likelihood of aseptic meningitis syndrome, because most enteroviral and arboviral infections occur in the summer or autumn in temperate climates (Bamberger et al, 2010).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Additional risk minimisation measures: None

CSF = cerebrospinal fluid; IVIg = intravenous immunoglobulin; ITP = primary immune thrombocytopenia; SmPC = Summary of Product Characteristics

Important Identified Risk 2: Haemolysis	
Evidence for linking the risk to the medicine	Clinical and post-marketing experience.
Risk factors and risk groups	Non-O blood group patients receiving high dose IVIg are at more risk of hemolysis. The anti-A and anti-B titer of the IVIg product used also appears to play a role, with products with an anti-A titer ≤ 1.16 (measured by direct method according to Ph. Eur.) rarely causing hemolysis (Bellac et al, 2015). Additional potential risk factors for patients developing ARF or DIC as a complication to IVIg-induced hemolysis include medical history of arterial hypertension, diabetes mellitus, age, sucrose (or sucrose-containing) IV preparations, nonhypogammaglobulinemic indications and chronic renal failure. Also patients exposed to drugs modifying the renal hemodynamic such as: ACE-I or ARA, diuretics and nonsteroidal anti-inflammatory drugs (Dickenmann et al, 2008; Lin et al, 2011; Moulis et al, 2011; Onuigbo et al, 2012).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Additional risk minimisation measures: None

ACE = angiotensin converting enzyme; ARF = acute renal failure; DIC = disseminated intravascular coagulopathy; IVIg = intravenous immunoglobulin; Ph. Eur. = European Pharmacopoeia; SmPC = Summary of Product Characteristics

Important Identified Risk 3: Hypersensitivity and anaphylactic reactions	
Evidence for linking the risk to the medicine	Clinical and post-marketing experience.
Risk factors and risk groups	Privigen may present an increased risk of anaphylaxis in IgA deficient patients as it contains traces of IgA. Although the role of IgA in anaphylactic reactions is controversial (Sandler et al, 2015). It is not anticipated that the risk of allergic / hypersensitivity / anaphylactic reactions be any different to other IVIg products. Privigen has a low IgA content (≤ 0.025 mg/ml), compared to most other IVIg products. General factors that increase the likelihood of Type 1 hypersensitivity include repeated exposure to the drug and a history of hypersensitivity to a drug of the same chemical class (Lenz, 2007).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Additional risk minimisation measures: None

IgA = immunoglobulin A; IVIg = intravenous immunoglobulin; SmPC = Summary of Product Characteristics

Important Identified Risk 4: Thromboembolic events	
Evidence for linking the risk to the medicine	Clinical and post-marketing experience.
Risk factors and risk groups	It has been suggested that older patients, patients with low cardiac output, and patients with atherosclerotic disease are at higher risk of side effects from increased serum viscosity (Brown and Ballas, 2003). However, thromboembolic events are believed to be rare in antibody-deficient patients receiving IVIg at replacement doses (200 to 600 mg/kg), as the increase in serum viscosity at such doses is minimal (Brown and Ballas, 2003). Patients with vascular risk factors or known vascular disease who require IVIg may be at an increased risk of development of thromboembolic phenomena, regardless of dose or autoimmune disease (Brown and Ballas, 2003). IVIg-treated neurologic patients may be more prone to strokes, as their long-standing muscle weakness, impaired mobility or wheelchair confinement could facilitate a subclinical hypercoagulable state or formation of silent clots, especially in patients at high risk for vascular disease (Dalakas and Clark, 2003).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Additional risk minimisation measures: None

IVIg = intravenous immunoglobulin; SmPC = Summary of Product Characteristics

Important Identified Risk 5: Acute renal failure	
Evidence for linking the risk to the medicine	Literature and post-marketing experience.
Risk factors and risk groups	Due to the use of L-proline as a stabiliser in Privigen, the risk of renal dysfunction / failure is anticipated to be small. IVIg associated renal failure mostly occurs in patients with pre-existing conditions or those at increased risk of renal ADRs, such as patients with prior renal insufficiency, diabetes mellitus, advanced age (> 65 years of age), dehydration or hypervolemia, sepsis, paraproteinemia or those concomitantly using other agents known to cause renal toxicity (Dantal et al, 2013). Acute renal failure can also occur as a complication of Haemolysis. This risk was substantially reduced with the reduction of spontaneous reports of hemolysis following the implementation of the IAC step into the manufacturing process of Privigen starting in 2016 (Shebl et al, 2018; Shebl et al, 2019).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Additional risk minimisation measures: None

ADR = adverse drug reaction; IAc = immunoaffinity chromatography; IVIg = intravenous immunoglobulin; SmPC = Summary of Product Characteristics

Important Potential Risk 1: Transfusion-related acute lung injury	
Evidence for linking the risk to the medicine	Literature and post-marketing experience.
Risk factors and risk groups	The incidence of TRALI is 50 to 100 times higher in critically ill patients than in the general population. Patients suffering from a clinical disorder such as sepsis are increasingly recognised as being at risk for development of TRALI (Vlaar and Juffermans, 2013).
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 and 4.8 Additional risk minimisation measures: None

SmPC = Summary of Product Characteristics; TRALI = transfusion-related acute lung injury

Important Potential Risk 2: Potential for transmission of infectious agents	
Evidence for linking the risk to the medicine	Literature. No evidence of a confirmed link of this risk with Privigen from different sources up to the DLP of the RMP.
Risk factors and risk groups	All patients treated with IVIg, although the risk is very low.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.4 Additional risk minimisation measures: None

DLP = data lock point; RMP = risk management plan; SmPC = Summary of Product Characteristics

Missing information 1: Neurotoxicity of L-proline in the paediatric population when used at high dose	
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Privigen.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Privigen.

Part VII: Annexes

Table of contents

Annex 4 Specific adverse drug reaction follow-up forms

Table of contents

Follow-up forms (see following pages)

Questionnaire on Aseptic Meningitis Syndrome (AMS) for Immunoglobulin Products

CSL EMPLOYEE/AFFILIATE USE ONLY

Global CSL Reference Number _____
Local tracking number: _____

Date of awareness of report (dd/mmm/yyyy): _____

☐ Initial report ☐ Follow up report

1. Patient Information

Patient Initials (First - Last)	**Date of Birth** (DD/MMM/YYYY)	**Age** (at event onset)	**Gender**	**Weight** (at event onset)	**Height** (at event onset)	**Race** (where local law allows)
		years Or Age Group	☐ Male ☐ Female	☐ kg ☐ lb	☐ cm ☐ in	☐ Asian ☐ Black ☐ Caucasian ☐ Aboriginal ☐ Torres Strait Is. ☐ Thai ☐ Nat Hawaiian ☐ Other (specify): _____

2. Suspect Drug Details

Product Name:	**Indication for Immunoglobulin therapy [diagnosis]:**	**Route of administration:**

Dosing regimen:

Dose 1 date:		Dose 2 date:		Dose 3 date:	
Dose:		Dose:		Dose:	
Start time:		Start time:		Start time:	
Stop time:		Stop time		Stop time	
Maximum IV infusion rate (mL/hr): OR SC Infusion rate for all sites in total (mL/hr):		Maximum IV infusion rate (mL/hr): OR SC infusion rate for all sites in total (mL/hr):		Maximum IV infusion rate (mL/hr): OR SC infusion rate for all sites in total (mL/hr):	
Lot Number(s):		Lot Number(s):		Lot Number(s):	

Provide additional doses as an attachment

3. Any relevant medical history?

Yes ☐ If yes, specify below No ☐ Unknown ☐

☐ Frequent headaches ☐ Migraine ☐ Previous episode(s) of AMS

Details if applicable (e.g., date of diagnosis, frequency, severity):

Previous immunoglobulin use: Yes ☐ No ☐
If yes, provide details of the therapy (e.g.: Brand name of the product, therapy start/ stop dates, dosing regimen, etc.):

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Clinical & Pharmacovigilance * 655 Elizabeth Street * Melbourne , Victoria Australia 3000 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Questionnaire on Aseptic Meningitis Syndrome (AMS) for Immunoglobulin Products

4. Any risk factors?	Yes ☐ If yes, specify below	No ☐	Unknown ☐
☐ Medical History (as above)	☐ High dose IVIG (2g/kg) If yes, enter in section 3.	☐ Rapid infusion rate If yes, enter in section 3.	
☐ Poor hydration on admission	☐ Headache prior to Ig administration		
Other Predisposing Factors?	Yes ☐ If yes, specify below	No ☐	Unknown ☐

5. Concomitant medications? Yes ☐ If yes, specify below No ☐ Unknown ☐

Drug	Dose and Frequency	Route	Indication for Use	Start date	Stop date

6. Did the patient receive pre-medication before the Ig infusion?	Yes ☐ If yes, specify below	No ☐	Unknown ☐
Name, dose, route, date and time of administration if applicable:			

7. Details of AMS (provide a clinical story of the event):

Event Onset Date & Time:	
Event Diagnosis:	
Presenting signs / symptoms:	☐ Severe headache ☐ Drowsiness ☐ Fever ☐ Nausea

☐ Nuchal rigidity ☐ Photophobia ☐ Painful eye movements ☐ Vomiting Other:

Event evolution:

8. Causality assessment to CSL product: ☐ Related ☐ Not Related ☐ Unknown

9. Lab results*:	Was a lumbar puncture performed? Yes ☐ No ☐ Unknown ☐
	If yes, date & time of lumbar puncture:

☐ Positive pleocytosis ☐ Elevated protein levels

Results:

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Clinical & Pharmacovigilance * 655 Elizabeth Street * Melbourne , Victoria Australia 3000 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Questionnaire on Aseptic Meningitis Syndrome (AMS) for Immunoglobulin Products

*Attach anonymised copies of relevant documentation (medical reports, exam/lab results, reference lab values, etc.).

10. Treatment of AMS (e. g., analgesia)?	Yes ☐ If yes, specify below	No ☐	Unknown ☐

11. Outcome of event:

Not recovered ☐ Recovered ☐ Recovering ☐ Unknown ☐ Fatal ☐

Recovered with sequelae ☐ *provide sequelae:*

Recovered with treatment ☐ *provide details:*

If patient recovered, provide date recovered (dd/mmm/yyyy):

☐ **No Further Information Available**

12. Reporter Information

This form also requests some information about you, the reporter/treating health care professional. This information will be used by CSL in conjunction with any follow up investigation of the event by CSL. This information may also be accessed by other members of the CSL Group of companies and relevant licencing partners (some of which are resident overseas) as part of CSL's global adverse event reporting database. If this information is not provided it may adversely affect our investigation. All personal data in this report will be kept protected and confidential in line with our Company Privacy Policy and data protection legislation (see Global Privacy Policy | CSL for Privacy Notice). The information provided will solely be used for pharmacovigilance obligations and may be reported in anonymized form to health authorities, where required by law. You have a right to access your personal data which we hold about you by contacting our Privacy Officer via email notification to privacy@cslbehring.com

Details of Reporter **Is this a consumer / patient report?** ☐ Yes ☐ No (If yes, has the patient given consent to CSL to follow up the adverse reaction report with the healthcare professional?) ☐ yes ☐ No If consent to follow up with healthcare professional was not given, does the patient give consent to CSL to be contacted regarding this adverse event report? ☐ Yes ☐ No	**Details of Treating Health Care Professional** (If different from Reporter)
Occupation:	Occupation:
Full Name:	Full Name:
Organisation/Address:	Organisation/Address:
Telephone: Fax	Telephone: Fax
Email:	Email:

Document Approvals

Approved Date: 13 Nov 2024

Task: Approval Task Verdict: Approve	PPD 04-Nov-2024 09:16:35 GMT+0000
Task: Approval Task Verdict: Approve	PPD 13-Nov-2024 01:39:41 GMT+0000
Task: QA Approval Verdict: Approve	PPD 13-Nov-2024 09:07:59 GMT+0000

Questionnaire for Haemolysis with Immunoglobulins

CSL EMPLOYEE/AFFILIATE USE ONLY

Global CSL Reference Number _____
Local tracking number: _____

Date of awareness of report (dd/mmm/yyyy): _____ ☐ Initial report ☐ Follow up report

1. Patient Information

Patient Initials (First - Last)	**Date of Birth** (DD/MMM/YYYY)	**Age** (at event onset)	**Gender**	**Weight** (at event onset)	**Height** (at event onset)	**Race** (where local law allows)
Blood Group		years Or Age Group	☐ Male ☐ Female	☐ kg ☐ lb	☐ cm ☐ in	☐ Asian ☐ Black ☐ Caucasian ☐ Aboriginal ☐ Torres Strait Is. ☐ Thai ☐ Nat Hawaiian ☐ Other (specify): _____

2. Relevant Medical History

Other relevant history (e.g. historical / pre-existing / current medical conditions (including allergies) / any medical procedure – provide dates)

Social history (e.g. smoking / alcohol / drug abuse / occupation)

3. Suspect Medicinal Product Information

Suspect Medicinal Product(s) (include all information available: trade name, generic name, strength and form a)	**Batch number(s)/ Lot number(s)**	**Indication(s) for use**
1.	1. ***Batch number unavailable?*** ☐	1.
2.	2. ***Batch number unavailable?*** ☐	2.

Has the product been stored correctly ☐ Yes ☐ No If no, specify:

Dose (with units)	**Frequency**	**Infusion rate (mL/hour)**	**Route of administration**
1.	1.	1.	1.
2.	2.	2.	2.

Current therapy dates related to this reported reaction(s) (dd/mmm/yyyy,) **From**	**To**	**Duration of therapy** (days/weeks/months)	**Action taken with Drug** (e.g. discontinued, maintained, reduced)	**Previous therapy with suspect medicinal product?**
1.	1.	1.	1.	1. ☐ Yes ☐ No ☐ Not applicable If yes, therapy dates (dd/mmm/yyyy) _____
2.	2.	2.	2.	2. ☐ Yes ☐ No ☐ Not applicable If yes, therapy dates (dd/mmm/yyyy) _____

* Continue on separate page if you need more space

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 1230 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL Melbourne * Global Safety & Pharmacovigilance * 655 Elizabeth Street Melbourne, Victoria Australia 3000 * Fax +61-3-9389-1095 * Email: Adverse.Events.Global@cslbehring.com

Questionnaire for Haemolysis with Immunogloblins

4. Investigations (including units and reference range)

	Prior to Immunoglobulin Treatment	Date and time of test	Post Immunoglobulin Treatment	Date and time of test
Haemoglobin				
Haptoglobin				
Lactate Dehydrogenase				
Reticulocytes				
Bilirubin Direct				
Bilirubin Indirect				
Was a Coombs test performed?	☐ Yes ☐ No Result: Date			
If Coombs test was positive, were antibodies eluted for specificity?	☐ Yes ☐ No Specificity:			
Signs and Symptoms	☐ Hepatosplenomegaly ☐ Dark Urine ☐ Other:			
All blood results:		***Attach an anonymised copy of the patient's blood results (including relevant laboratory investigations specific for haemolysis). Include units and reference range.***		

5. Patient outcome:

Not recovered ☐ Recovered ☐ Recovering ☐ Unknown ☐ Fatal ☐

Recovered with sequelae ☐ *provide sequelae:*

Recovered with treatment ☐ *provide details:*

If patient recovered, provide date recovered:

6. Management of the event (e.g. transfusion):

7. Concomitant medications?

Yes ☐ If yes, specify below No ☐ Unknown ☐

Drug	Dose and Frequency	Route	Indication for Use	Start date	Stop date

8. Causality assessment to CSL product:

☐ Related ☐ Not Related ☐ Unknown

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 1230 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL Melbourne * Global Safety & Pharmacovigilance * 655 Elizabeth Street Melbourne, Victoria Australia 3000 * Fax +61-3-9389-1095 * Email: Adverse.Events.Global@cslbehring.com

Questionnaire for Haemolysis with Immunoglobulins

☐ **No Further Information Available**

9. Reporter Information

This form also requests some information about you, the reporter/treating health care professional. This information will be used by CSL in conjunction with any follow up investigation of the event by CSL. This information may also be accessed by other members of the CSL Group of companies and relevant licencing partners (some of which are resident overseas) as part of CSL's global adverse event reporting database. If this information is not provided it may adversely affect our investigation. All personal data in this report will be kept protected and confidential in line with our Company Privacy Policy and data protection legislation (see Global Privacy Policy | CSL for Privacy Notice). The information provided will solely be used for pharmacovigilance obligations and may be reported in anonymized form to health authorities, where required by law. You have a right to access your personal data which we hold about you by contacting our Privacy Officer via email notification to privacy@cslbehring.com

Details of Reporter **Is this a consumer / patient report?** ☐ Yes ☐ No (If yes, has the patient given consent to CSL to follow up the adverse reaction report with the healthcare professional?) ☐ Yes ☐ No If consent to follow up with healthcare professional was not given, does the patient give consent to CSL to be contacted regarding this adverse event report? ☐ Yes ☐ No	**Details of Treating Health Care Professional** (If different from Reporter)
Occupation:	Occupation:
Full Name:	Full Name:
Organisation/Address:	Organisation/Address:
Telephone: Fax	Telephone: Fax
Email:	Email:

Document Approvals

Approved Date: 13 Nov 2024

Task: Approval Task Verdict: Approve	PPD 04-Nov-2024 09:16:35 GMT+0000
Task: Approval Task Verdict: Approve	PPD 13-Nov-2024 01:39:41 GMT+0000
Task: QA Approval Verdict: Approve	PPD 13-Nov-2024 09:07:59 GMT+0000

Questionnaire on Allergic / Anaphylactic Reactions for all Products

CSL EMPLOYEE/AFFILIATE USE ONLY	
Global CSL Reference Number _____ Local tracking number: _____	
Date of awareness of report (dd/mmm/yyyy): _____	☐ Initial report ☐ Follow up report

1. Patient Information

Patient Initials (First - Last)	**Date of Birth (DD/MMM/YYYY)**	**Age** (at event onset) years Or Age Group	**Gender** ☐ Male ☐ Female	**Weight** (at event onset) ☐ kg or ☐ lb	**Height** (at event onset) ☐ cm or ☐ in	**Race (where local law allows)** ☐ Asian ☐ Black ☐ Caucasian ☐ Aboriginal ☐ Torres Strait Is. ☐ Thai ☐ Nat Hawaiian ☐ Other (specify): _____

2. Patient History

Does the patient have any previous history of allergic reactions or hypersensitivity to:

Animal Hair?	Yes ☐	No ☐
Allergy to arthropod sting?	Yes ☐	No ☐
Food?	Yes ☐	No ☐
Seasonal allergy?	Yes ☐	No ☐
Medication?	Yes ☐	No ☐
Other?	Yes ☐	No ☐

If 'yes' for any of the above, specify:

Does the patient have any previous history of:

Atopic dermatitis?	Yes ☐	No ☐
Extrinsic asthma?	Yes ☐	No ☐
Allergic rhinitis?	Yes ☐	No ☐
Other?	Yes ☐	No ☐

If 'yes' for any of the above, specify:

Does the patient have a family history of allergic predisposition (atopic disorders, etc.)? Yes ☐ No ☐

If 'yes', specify:

What is the patient's occupation?:

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Safety & Pharmacovigilance * 655 Elizabeth Street * Melbourne , Victoria Australia 3000 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Questionnaire on Allergic / Anaphylactic Reactions for all Products

Concomitant/ Confounding Factors:

Alcohol?	Yes ☐	No ☐
Infections?	Yes ☐	No ☐
Medication?	Yes ☐	No ☐
Menstruation?	Yes ☐	No ☐
Physical strain?	Yes ☐	No ☐
Stress?	Yes ☐	No ☐
Other?	Yes ☐	No ☐

If 'yes' for any of the above, specify:

3. Previous Exposure to Medicinal Products with Same Active Ingredient

Has the patient previously been treated with either the same CSL product or other products containing the same active ingredient? Yes ☐ No ☐ Unknown ☐

If 'yes':

- Provide the therapy dates / total exposure. Specify the name of the product as well as the batch number along with the dates*:
- Were previous product administrations/ applications tolerated? Yes ☐ No ☐

  If 'no', describe symptoms and therapeutic measures:

4. Medicinal Product Exposure

Provide all therapy dates with CSL product(s) prior to onset of the symptoms of allergic / anaphylactic reaction, including batch numbers and exact dosage of each single administration:

Product(s):	Batch no and exact dosage(s):	Exact therapy dates (dd/mmm/yyyy):

Time interval between administration and onset of the allergic / anaphylactic reaction (specify in minutes, hours etc):

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Safety & Pharmacovigilance * 655 Elizabeth Street * Melbourne , Victoria Australia 3000 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Questionnaire on Allergic / Anaphylactic Reactions for all Products

5. Information on the allergic / anaphylactic reaction - Did patient exhibit any of the following symptoms:

Skin:

- Flush	Yes ☐	No ☐
- Pruritus (itching)	Yes ☐	No ☐
- Rash	Yes ☐	No ☐
- Swelling of face / angioedema	Yes ☐	No ☐
- Urticaria	Yes ☐	No ☐
- Erythema	Yes ☐	No ☐
- Eczema	Yes ☐	No ☐

- Other skin lesions, e.g. macules, papules, purpura, blister, pustules (please specify type, location):
- Other?, specify:

Circulatory System, and Nervous System:

- Circulatory failure	Yes ☐	No ☐
- Dizziness	Yes ☐	No ☐
- Syncope	Yes ☐	No ☐
- Hypotension	Yes ☐	No ☐
- Tachycardia	Yes ☐	No ☐
- Loss of consciousness	Yes ☐	No ☐
- Cardiac arrest	Yes ☐	No ☐

- Other?, specify:

Gastrointestinal System:

- Abdominal pain	Yes ☐	No ☐
- Diarrhea	Yes ☐	No ☐
- Stool incontinence	Yes ☐	No ☐
- Nausea	Yes ☐	No ☐
- Nausea	Yes ☐	No ☐
- Vomiting	Yes ☐	No ☐

- Other?, specify:

Mucosa:

- Prickling or tingling of mouth	Yes ☐	No ☐
- Lip swelling,	Yes ☐	No ☐
- Swollen tongue	Yes ☐	No ☐
- Pharyngeal swelling	Yes ☐	No ☐

- Other?, specify:

Respiratory System:

- Cough	Yes ☐	No ☐
- Respiratory arrest	Yes ☐	No ☐
- Respiratory distress	Yes ☐	No ☐
- Shortness of breath	Yes ☐	No ☐
- Hyperventilation	Yes ☐	No ☐
- Bronchospasm	Yes ☐	No ☐
- Wheezing	Yes ☐	No ☐

- Other?, specify:

Other / general symptoms:

Feeling of impending doom	Yes ☐	No ☐
Chills, Rigors	Yes ☐	No ☐
Urine incontinence	Yes ☐	No ☐

Other?, specify:

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Safety & Pharmacovigilance * 655 Elizabeth Street * Melbourne , Victoria Australia 3000 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Questionnaire on Allergic / Anaphylactic Reactions for all Products

Were symptoms considered to be part of an anaphylactic reaction:	Yes ☐ No ☐
If applicable, provide any alternative diagnosis:	

6. Laboratory confirmation of allergic / anaphylactic reaction (including measurements of vital signs) if applicable:

Measurement	Result	Units/Normal range if applicable	Date and Time
Blood Pressure			
Heart Rate			
Respiratory Rate			
Total IgE			
Specific RAST (Radioallergosorbent test)			
Skin Prick Test			
Serum Mast Cell Tryptase			
Other:			

7. Concomitant medications? (exclude those used to treat reaction)	Yes ☐ If yes, specify below No ☐ Unknown ☐

Drug	Dose	Route	Indication for Use	Start date	Stop date

8. Treatment and Outcome

Describe therapeutic measures (e.g. antihistamines, steroids, epinephrine, ß2-agonists, including route of administration (IV, IM, inhaler); venous access; hospitalisation etc.):

Outcome:

Not recovered ☐ Recovered ☐ Recovering ☐ Fatal ☐ Unknown ☐

Recovered with sequelae ☐ *provide sequelae:*

Recovered with treatment ☐ *provide details:*

If patient recovered, provide date recovered:

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Safety & Pharmacovigilance * 655 Elizabeth Street * Melbourne , Victoria Australia 3000 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Questionnaire on Allergic / Anaphylactic Reactions for all Products

9. Additional Medication of the Patient				
Will the patient continue with CSL products?	Yes ☐	No ☐		
Will the patient be premedicated prior to further administrations?	Yes ☐	No ☐		
If 'yes', specify				

10. Causality assessment to CSL product: ☐ Related ☐ Not Related ☐ Unknown

☐ **No Further Information Available**

11. Reporter Information

*This form also requests some information about you, the reporter/treating health care professional. This information will be used by CSL in conjunction with any follow up investigation of the event by CSL. This information may also be accessed by other members of the CSL Group of companies and relevant licencing partners (some of which are resident overseas) as part of CSL's global adverse event reporting database. If this information is not provided it may adversely affect our investigation. All personal data in this report will be kept protected and confidential in line with our Company Privacy Policy and data protection legislation (see **https://privacy.csl.com/pv-medinfo-pqc** for Privacy Notice). The information provided will solely be used for pharmacovigilance obligations and may be reported in anonymized form to health authorities, where required by law. You have a right to access your personal data which we hold about you by contacting our Privacy Officer via email notification to privacy@cslbehring.com*

Details of Reporter **Is this a consumer / patient report?** ☐ Yes ☐ No (If yes, has the patient given consent to CSL to follow up the adverse reaction report with the healthcare professional?) ☐ yes ☐ No If consent to follow up with healthcare professional was not given, does the patient give consent to CSL to be contacted regarding this adverse event report? ☐ Yes ☐ No	**Details of Treating Health Care Professional** (If different from Reporter)
Occupation:	Occupation:
Full Name:	Full Name:
Organisation/Address:	Organisation/Address:
Telephone: Fax	Telephone: Fax
Email:	Email:

Document Approvals
Approved Date: 07 Apr 2025

Task: Approval Task Verdict: Approve	PPD 04-Apr-2025 02:04:50 GMT+0000
Task: Approval Task Verdict: Approve	PPD A 04-Apr-2025 07:43:22 GMT+0000
Task: QA Approval Verdict: Approve	PPD Q 07-Apr-2025 21:24:33 GMT+0000

Generated by PPD on 21 Jan 2026 at 08:32PM GMT-05:00

Questionnaire on Thromboembolic Events (TEE)

CSL EMPLOYEE/AFFILIATE USE ONLY

Global CSL Reference Number _____
Local tracking number: _____

Date of awareness of report (dd/mmm/yyyy): _____

☐ Initial report ☐ Follow up report

1. Patient Information

Patient Initials (First - Last)	**Date of Birth** (DD/MMM/YYYY)	**Age** (at event onset)	**Gender**	**Weight** (at event onset)	**Height** (at event onset)	**Race** (where local law allows)
		years Or Age Group	☐ Male ☐ Female	☐ kg ☐ lb	☐ cm ☐ in	☐ Asian ☐ Black ☐ Caucasian ☐ Aboriginal ☐ Torres Strait Is. ☐ Thai ☐ Nat Hawaiian ☐ Other (specify): _____

2. Patient History / Concomitant Diseases / Concomitant Factors

Does the patient have any known previous history of or currently suffer from:

Autoantibody diseases (e.g. antiphospholipid syndrome, lupus erythematosus, collagen-vascular diseases)?	Yes ☐	No ☐
Cerebrovascular accident / Transient Ischemic Attack?	Yes ☐	No ☐
Hypertension?	Yes ☐	No ☐
Nephrotic syndrome	Yes ☐	No ☐
Inflammatory bowel disease?	Yes ☐	No ☐
Malignant diseases / Carcinoma?	Yes ☐	No ☐
Myocardial infarction / Coronary artery disease?	Yes ☐	No ☐
Valvular heart disease?	Yes ☐	No ☐
Polycythemia vera?	Yes ☐	No ☐
Pulmonary embolism?	Yes ☐	No ☐
Recent sepsis?	Yes ☐	No ☐
Recent shock?	Yes ☐	No ☐
Surgical interventions in the past 6 months?	Yes ☐	No ☐
Trauma of lower extremity, hip, abdomen or pelvis	Yes ☐	No ☐
Thrombogenic mutations (FV Leiden, Hyperhomocysteinemia, protein C deficiency, protein S deficiency, antithrombin deficiency, increase of plasminogen activator inhibitor (PAI-1), prothrombin mutation, etc.)?	Yes ☐	No ☐
Thrombophlebitis?	Yes ☐	No ☐
Deep Vein Thrombosis?	Yes ☐	No ☐
Varicosis?	Yes ☐	No ☐
Obesity?	Yes ☐	No ☐
Dehydration?	Yes ☐	No ☐
Hormone Replacement Therapy?	Yes ☐	No ☐
Immobilization?	Yes ☐	No ☐

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Safety & Pharmacovigilance * 655 Elizabeth Street * Melboune , Victoria Australia 3000 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Questionnaire on Thromboembolic Events (TEE)

2. Patient History / Concomitant Diseases / Concomitant Factors

Oral Contraceptives?	Yes ☐	No ☐
Smoking?	Yes ☐	No ☐
Steroid therapy?	Yes ☐	No ☐
Arterial / Venous Catheters?	Yes ☐	No ☐

If 'yes' to any of the above, further specify*:

Does the patient have a known family history of TEEs? Yes ☐ No ☐

If yes, specify:

3. Previous Exposure to Plasma Derived (or Recombinant) Medicinal Products

Had the patient previously been treated with either the same CSL product or other products containing the same active ingredient? Yes ☐ No ☐

If 'yes', provide the therapy dates / total exposure. Specify the name of the product as well as the batch number*:

Have previous applications of the same CSL product or another product containing the same active ingredient been tolerated well? Yes ☐ No ☐

If 'no', describe symptoms and therapeutic measures*:

These questions apply ONLY if Voncento / Biostate / Haemate P / Humate P was used:

- Age of patient when first treated with Voncento / Biostate/Haemate P/Humate P: years
- Age of patient when first treated with other factor VIII / VWF products: years

4. Current Medicinal Product Exposure

Provide all therapy dates with CSL product(s) prior to onset of the TEE, including batch numbers and exact dosage of each single administration:

Product(s):	Batch no(s):	Exact dosage:	Exact therapy dates (dd/mmm/yyyy):

Provide the last known INR value prior to product administration:

INR: Date of measurement: (dd/mmm/yyyy)

Time interval between administration and onset / diagnosis of TEE:

Therapy dates (dd/mmm/yyyy):	Onset of the adverse reaction (dd/mmm/yyyy):

* Continue on separate page if you need more space

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Safety & Pharmacovigilance * 655 Elizabeth Street * Melboune , Victoria Australia 3000 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Questionnaire on Thromboembolic Events (TEE)

5. **Concomitant medications?** (with special reference to products known to be associated with TEE)	Yes ☐ If yes, specify below	No ☐	Unknown ☐

Drug	Dose and Frequency	Route	Indication for Use	Start date	Stop date

6. Details of TEE, provide a clinical story of the event:

7. Laboratory results

Provide information on the following laboratory values	Prior to Event (including date & time)	At onset of Event (including date & time)	Units	Reference range
D-dimers				
INR				
Thromboplastin time (or Quick value)				
aPTT				
Thrombin time				
Fibrinogen				
Fibrin monomers				
TAT complexes				

Was thrombosis / embolism confirmed by ultrasound, phlebography, CT scan, V/P scintigraphy, echocardiography etc? Yes ☐ No ☐

If 'yes', specify*:

8. Treatment of adverse event / adverse reaction

Indicate therapeutic measures, e.g. medication [heparins (UFH, LMWH), thrombolytics etc.], surgical intervention:

9. Outcome of event

Not recovered ☐ Recovered ☐ Recovering ☐ Unknown ☐ Fatal ☐

Recovered with sequelae ☐ *provide sequelae:*

Recovered with treatment ☐ *provide details:*

If patient recovered, provide date recovered:

Will the patient continue with CSL products ?

* Continue on separate page if you need more space

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Safety & Pharmacovigilance * 655 Elizabeth Street * Melboune , Victoria Australia 3000 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Questionnaire on Thromboembolic Events (TEE)

10. Causality assessment to CSL product:	☐ Related ☐ Not Related ☐ Unknown

☐ **No Further Information Available**

11. Reporter Information

This form also requests some information about you, the reporter/treating health care professional. This information will be used by CSL in conjunction with any follow up investigation of the event by CSL. This information may also be accessed by other members of the CSL Group of companies and relevant licencing partners (some of which are resident overseas) as part of CSL's global adverse event reporting database. If this information is not provided it may adversely affect our investigation. All personal data in this report will be kept protected and confidential in line with our Company Privacy Policy and data protection legislation (see Global Privacy Policy | CSL for Privacy Notice). The information provided will solely be used for pharmacovigilance obligations and may be reported in anonymized form to health authorities, where required by law. You have a right to access your personal data which we hold about you by contacting our Privacy Officer via email notification to privacy@cslbehring.com

Details of Reporter **Is this a consumer / patient report?** ☐ Yes ☐ No (If yes, has the patient given consent to CSL to follow up the adverse reaction report with the healthcare professional?) ☐ Yes ☐ No If consent to follow up with healthcare professional was not given, does the patient give consent to CSL to be contacted regarding this adverse event report? ☐ Yes ☐ No	**Details of Treating Health Care Professional** (If different from Reporter)
Occupation:	Occupation:
Full Name:	Full Name:
Organisation/Address:	Organisation/Address:
Telephone: Fax	Telephone: Fax
Email:	Email:

Document Approvals

Approved Date: 13 Nov 2024

Task: Approval Task Verdict: Approve	PPD 04-Nov-2024 09:16:35 GMT+0000
Task: Approval Task Verdict: Approve	PPD 13-Nov-2024 01:39:41 GMT+0000
Task: QA Approval Verdict: Approve	PPD 13-Nov-2024 09:07:59 GMT+0000

Questionnaire on Acute Renal Failure (ARF) after Immunoglobulin (IG) Therapy

CSL EMPLOYEE/AFFILIATE USE ONLY

Global CSL Reference Number +_____
Local tracking number: _____

Date of awareness of report (dd/mmm/yyyy): _____ ☐ Initial report ☐ Follow up report

1. Patient Information

Patient Initials (First - Last)	**Date of Birth** (DD/MMM/YYYY)	**Age** (at event onset)	**Gender**	**Weight** (at event onset)	**Height** (at event onset)	**Race** (where local law allows)
		years Or Age Group	☐ Male ☐ Female	☐ kg ☐ lb	☐ cm ☐ in	☐ Asian ☐ Black ☐ Caucasian ☐ Aboriginal ☐ Torres Strait Is. ☐ Thai ☐ Nat Hawaiian ☐ Other (specify): _____

2. Patient History

Diabetes Mellitus	Yes ☐	No ☐	Unknown ☐
Hypertension	Yes ☐	No ☐	Unknown ☐
Renal Insufficiency	Yes ☐ If yes, specify below	No ☐	Unknown ☐
When was the renal insufficiency diagnosed for the first time?			
What was the (suspected) cause of renal insufficiency?			
Prior creatinine value (value, units, normal ranges, and date)?			
Attach anonymized copies of relevant documentation (medical report, results, laboratory findings, expert's report)			

3. Suspect drug details

Product Name:		**Indication**		**Route of administration:**	
Dosing regimen:					
Dose 1 date (DD/MMM/YYYY):		Dose 2 date (DD/MMM/YYYY):		Dose 3 date (DD/MMM/YYYY):	
Dose:		Dose:		Dose:	
Start time:		Start time:		Start time:	
Stop time:		Stop time		Stop time	
Maximum IV infusion rate (mL/hr): OR SC Infusion rate for all sites in total (mL/hr)		Maximum IV infusion rate (mL/hr): OR SC Infusion rate for all sites in total (mL/hr)		Maximum IV infusion rate (mL/hr): OR SC Infusion rate for all sites in total (mL/hr)	
Lot Number(s):		Lot Number(s):		Lot Number(s):	

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Safety & Pharmacovigilance * 655 Elizabeth Street * Melbourne, Victoria Australia 3000 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Questionnaire on Acute Renal Failure (ARF) after Immunoglobulin (IG) Therapy

4. Cumulative and daily dose of IG (reported as total grams, g/kg, % solution, and infusion volume)

Date ((DD/MMM/YYYY)	Daily Dose	Cumulative Dose

5. Concomitant medications (including those that are nephrotoxic)?

Yes ☐ If yes, specify below No ☐ Unknown ☐

Drug	Dose and Frequency	Route	Indication for Use	Start date ((DD/MMM/YYYY)	Stop date ((DD/MMM/YYYY)

6. Details of ARF. Provide the clinical course / symptoms of the ARF post IG, including time intervals (e.g. pulmonary edema, oliguria):

Comment on other contributing factors besides Ig administration:

7. Was a renal biopsy carried out?

Yes ☐ If yes, specify below No ☐ Unknown ☐

Results	Date	

8. Laboratory results

Course of serum creatinine level
Reference range:

Date / Time (DD/MMM/YYYY)	Level	Units (µmol/L or mg/dL)

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Safety & Pharmacovigilance * 655 Elizabeth Street * Melbourne, Victoria Australia 3000 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Questionnaire on Acute Renal Failure (ARF) after Immunoglobulin (IG) Therapy

8. Laboratory results

Other relevant laboratory results (e. g. 24-hr urine volume, serum potassium):

Date/Time (DD/MMM/YYYY)	Test Name	Results with units	Reference range

9. Treatment of ARF (e. g., diuretics, dialysis)

Yes ☐ If yes, specify below No ☐ Unknown ☐

10. Outcome of event

Not recovered ☐ Recovered ☐ Recovering ☐ Unknown ☐ Fatal ☐

Recovered with sequelae ☐ *provide sequelae:*

Recovered with treatment ☐ *provide details:*

If patient recovered, provide date recovered:

If fatal outcome, was an autopsy carried out? Yes ☐ No ☐ Unknown ☐

If yes, provide the autopsy report

Autopsy results, especially renal histology: **Date** (DD/MMM/YYYY)

11. Causality assessment to CSL product: ☐ Related ☐ Not Related ☐ Unknown

☐ **No Further Information Available**

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Safety & Pharmacovigilance * 655 Elizabeth Street * Melbourne, Victoria Australia 3000 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Questionnaire on Acute Renal Failure (ARF) after Immunoglobulin (IG) Therapy

12. Reporter Information

This form also requests some information about you, the reporter/treating health care professional. This information will be used by CSL in conjunction with any follow up investigation of the event by CSL. This information may also be accessed by other members of the CSL Group of companies and relevant licencing partners (some of which are resident overseas) as part of CSL's global adverse event reporting database. If this information is not provided it may adversely affect our investigation. All personal data in this report will be kept protected and confidential in line with our Company Privacy Policy and data protection legislation (see Global Privacy Policy | CSL for Privacy Notice). The information provided will solely be used for pharmacovigilance obligations and may be reported in anonymized form to health authorities, where required by law. You have a right to access your personal data which we hold about you by contacting our Privacy Officer via email notification to privacy@cslbehring.com

Details of Reporter **Is this a consumer / patient report?** ☐ Yes ☐ No (If yes, has the patient given consent to CSL to follow up the adverse reaction report with the healthcare professional?) ☐ yes ☐ No If consent to follow up with healthcare professional was not given, does the patient give consent to CSL to be contacted regarding this adverse event report? ☐ Yes ☐ No	**Details of Treating Health Care Professional** (If different from Reporter)
Occupation:	Occupation:
Full Name:	Full Name:
Organisation/Address:	Organisation/Address:
Telephone: Fax	Telephone: Fax
Email:	Email:

Document Approvals

Approved Date: 13 Nov 2024

Task: Approval Task Verdict: Approve	PPD 04-Nov-2024 09:16:35 GMT+0000
Task: Approval Task Verdict: Approve	PPD 13-Nov-2024 01:39:41 GMT+0000
Task: QA Approval Verdict: Approve	PPD 13-Nov-2024 09:07:59 GMT+0000

Questionnaire on Transfusion Related Acute Lung Injury (TRALI)

CSL EMPLOYEE/AFFILIATE USE ONLY	
Global CSL Reference Number _____ Local tracking number: _____	
Date of awareness of report (dd/mmm/yyyy): _____	☐ Initial report ☐ Follow up report

1. Patient Information

Patient Initials (First - Last)	**Date of Birth** (DD/MMM/YYYY)	**Age** (at event onset)	**Gender**	**Weight** (at event onset)	**Height** (at event onset)	**Race** (where local law allows)
		years Or Age Group	☐ Male ☐ Female	☐ kg ☐ lb	☐ cm ☐ in	☐ Asian ☐ Black ☐ Caucasian ☐ Aboriginal ☐ Torres Strait Is. ☐ Thai ☐ Nat Hawaiian ☐ Other (specify): _____

2. Patient History / Concomitant Diseases / Concomitant Factors

Does the patient have any known recent history of or currently suffer from:

Aspiration Pneumonia?	*Yes* ☐	*No* ☐
Cardiac Disease?	*Yes* ☐	*No* ☐
Coronary Artery Disease?	*Yes* ☐	*No* ☐
Lung Transplant?	*Yes* ☐	*No* ☐
Inhalation injury?	*Yes* ☐	*No* ☐
Lung contusion?	*Yes* ☐	*No* ☐
Multiple Injuries?	*Yes* ☐	*No* ☐
Thermal Burn ?	*Yes* ☐	*No* ☐
Chemical Burn?	*Yes* ☐	*No* ☐
Cardiopulmonary bypass?	*Yes* ☐	*No* ☐
Pulmonary/Lung embolism?	*Yes* ☐	*No* ☐
Recent sepsis?	*Yes* ☐	*No* ☐
Recent shock?	*Yes* ☐	*No* ☐
Acute pancreatitis?	*Yes* ☐	*No* ☐
Fluid overload?	*Yes* ☐	*No* ☐
Haematological malignancy?	*Yes* ☐	*No* ☐
Massive transfusion?	*Yes* ☐	*No* ☐

If 'yes' to any of the above, specify further:

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Safety & Pharmacovigilance * 655 Elizabeth Street * Melbourne , Victoria Australia 3000 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Questionnaire on Transfusion Related Acute Lung Injury (TRALI)

3. Suspect Medicinal Product Information

Product Name:		**Indication [diagnosis]:**			
Dosing regimen:					
Dose 1 date:		Dose 2 date:		Dose 3 date:	
Dose:		Dose:		Dose:	
Start time:		Start time:		Start time:	
Stop time:		Stop time		Stop time	
Route of Administration		Route of Administration		Route of Administration	
Maximum infusion rate (mL/hr):		Maximum infusion rate (mL/hr):		Maximum infusion rate (mL/hr):	
Lot Number(s):		Lot Number(s):		Lot Number(s):	

4. Other Blood products administered to the patient?

Yes ☐ If yes, specify below No ☐

Specify Blood Product	Dose and Frequency	Route	Indication for Use	Start date / time	Stop date / time

5. Concomitant medications?

Yes ☐ If yes, specify below No ☐ Unknown ☐

Drug	**Dose and Frequency**	**Route**	**Indication for Use**	**Start date**	**Stop date**

6. Details of TRALI (provide a clinical story of the event):

Event Onset:	Date & Time: Within 6 hours of receiving CSL product Yes ☐ No ☐ Within 6-72 hours of receiving CSL product Yes ☐ No ☐ If Yes, specify exact time interval
Presenting signs/symptoms:	☐ Dyspnea ☐ Cyanosis ☐ Fever ☐ Hypoxemia ☐ Tachypnoea ☐ Hypotension ☐ Leukopenia ☐ Thrombopenia Other:
Differential Diagnosis:	Transfusion Associated Circulatory Overload (TACO) Yes ☐ No ☐ Acute Respiratory Distress Syndrome (ARDS) Yes ☐ No ☐ Pulmonary Edema with a cardiac origin Yes ☐ No ☐ Non-specific Pulmonary Edema Yes ☐ No ☐

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Safety & Pharmacovigilance * 655 Elizabeth Street * Melbourne , Victoria Australia 3000 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Questionnaire on Transfusion Related Acute Lung Injury (TRALI)

	Other potential diagnoses:
Causality Assessment to CSL Product	☐ Related ☐ Not Related ☐ Unknown

7. Investigation results*:	**Date and Time**
Chest X-Ray:	
CT Thorax:	
ECG:	
Echocardiogram:	
Oxygen saturation:	
PaO2/FiO2:	
Pulmonary artery wedge pressure:	
Thrombocyte/ Leukocyte Counts (units and reference range)	
Other, specify:	

****If more convenient, attach anonymised copies of relevant documentation (medical reports, exam / lab results, reference lab values, etc.).***

8. Treatment of TRALI? Yes ☐ If yes, specify below No ☐ Unknown ☐

9. Outcome of event:

☐ Not recovered ☐ Recovered ☐ Recovering ☐ Unknown ☐ Fatal

Recovered with sequelae ☐ *provide sequelae :* Recovered with treatment ☐ *provide details :*

If patient recovered, provide date recovered:

10. Causality assessment to CSL product: ☐ Related ☐ Not Related ☐ Unknown

☐ **No Further Information Available**

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Safety & Pharmacovigilance * 655 Elizabeth Street * Melbourne , Victoria Australia 3000 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Questionnaire on Transfusion Related Acute Lung Injury (TRALI)

11. Reporter Information

This form also requests some information about you, the reporter/treating health care professional. This information will be used by CSL in conjunction with any follow up investigation of the event by CSL. This information may also be accessed by other members of the CSL Group of companies and relevant licencing partners (some of which are resident overseas) as part of CSL's global adverse event reporting database. If this information is not provided it may adversely affect our investigation. All personal data in this report will be kept protected and confidential in line with our Company Privacy Policy and data protection legislation (see Global Privacy Policy | CSL for Privacy Notice). The information provided will solely be used for pharmacovigilance obligations and may be reported in anonymized form to health authorities, where required by law. You have a right to access your personal data which we hold about you by contacting our Privacy Officer via email notification to privacy@cslbehring.com

Details of Reporter **Is this a consumer / patient report?** ☐ Yes ☐ No (If yes, has the patient given consent to CSL to follow up the adverse reaction report with the healthcare professional?) ☐ Yes ☐ No If consent to follow up with healthcare professional was not given, does the patient give consent to CSL to be contacted regarding this adverse event report? ☐ Yes ☐ No	**Details of Treating Health Care Professional** (If different from Reporter)
Occupation:	Occupation:
Full Name:	Full Name:
Organisation/Address:	Organisation/Address:
Telephone: Fax	Telephone: Fax
Email:	Email:

Document Approvals

Approved Date: 13 Nov 2024

Task: Approval Task Verdict: Approve	PPD 04-Nov-2024 09:16:35 GMT+0000
Task: Approval Task Verdict: Approve	PPD 13-Nov-2024 01:39:41 GMT+0000
Task: QA Approval Verdict: Approve	PPD 13-Nov-2024 09:07:59 GMT+0000

Questionnaire on Transmission of Infectious Agents

CSL EMPLOYEE/AFFILIATE USE ONLY

Global CSL Reference Number _____
Local tracking number: _____

Date of awareness of report (dd/mmm/yyyy): _____

☐ Initial report ☐ Follow up report

1. Patient Information

Patient Initials (First - Last)	**Date of Birth** (DD/MMM/YYYY)	**Age** (at event onset)	**Gender**	**Weight** (at event onset)	**Height** (at event onset)	**Race** (where local law allows)
		years Or Age Group	☐ Male ☐ Female	☐ kg ☐ lb	☐ cm ☐ in	☐ Asian ☐ Black ☐ Caucasian ☐ Aboriginal ☐ Torres Strait Is. ☐ Thai ☐ Nat Hawaiian ☐ Other (specify): _____

2. Details of Suspect Drug

Drug Name:	Indication for use:	Route of administration: **IV** ☐ **IM** ☐ **SC** ☐ Other (specify)

3. Dates of Suspect Drug Administration

Dose 1		Dose 2		Dose 3		Dose 4	
Date (dd/mmm/yyyy)		**Date (dd/mmm/yyyy)**		**Date (dd/mmm/yyyy)**		**Date (dd/mmm/yyyy)**	
Dose / Frequency		**Dose / Frequency**		**Dose / Frequency**		**Dose / Frequency**	
Total exposure days		**Total exposure days**		**Total exposure days**		**Total exposure days**	
Lot Number		**Lot Number**		**Lot Number**		**Lot Number**	

Is / Are other drug(s)/blood product(s) co-suspected? **Yes** ☐ **No** ☐
(if yes provide details)*:

Other Suspect Drug / Blood Product	**Dose**	**Route**	**Indication for Use**	**Start date**	**Stop date**

* Continue on separate page if you need more space.

4. Adverse Event

What infection is suspected of being transmitted (indicate)?

Hepatitis ..... Yes ☐ No ☐
If yes, specify (i.e. B, or C):
HIV ..... Yes ☐ No ☐
Parvovirus B19..... Yes ☐ No ☐

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Safety & Pharmacovigilance * 655 Elizabeth Street * Melbourne , Victoria Australia 3000 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Questionnaire on Transmission of Infectious Agents

4. Adverse Event

Prion	Yes ☐	No ☐
Other?	Yes ☐	No ☐
If 'yes' for Other, specify:		
Date diagnosed:		
Type of test(s) performed (also enter in **Section 9**):		
Did the patient have any presenting illness (clinical symptoms of infection)?	Yes ☐	No ☐
If yes, provide details:		
Is the occurrence of event causally related to the product administration?	Yes ☐	No ☐
Specify		

5. Causality assessment to CSL product:

☐ Related ☐ Not Related ☐ Unknown

6. Event outcome

Not recovered ☐ Recovered ☐ Recovering ☐ Unknown ☐ Fatal ☐

Recovered with sequelae ☐ *provide sequelae:*

Recovered with treatment ☐ *provide details:*

If patient recovered, provide date recovered:

7. Medical History and Risk Factors

Does the patient have any relevant / significant past medical history:	Yes ☐	No ☐
If yes, provide details:		
Was serology for **infection** performed prior to suspect drug intake:	Yes ☐	No ☐
If yes, provide details (also enter in **Section 9**):		
Was patient vaccinated against Hepatitis in the past:	Yes ☐	No ☐
If yes, provide dates and type (hepatitis A and/or B) of vaccination:		
Was a Liver Function Test (LFT) including liver enzymes performed prior to suspect drug intake?	Yes ☐	No ☐
If yes, provide details or attach copy of results:		
Did the patient have the following known risk factors for Infection?	***If yes, provide details***	
Occupation - Health Care Professional:	Yes ☐	No ☐
History of contact with person with illness or known carrier:	Yes ☐	No ☐
Recent overseas travel:	Yes ☐	No ☐
IV Drug use / Needle sharing:	Yes ☐	No ☐
Blood Transfusion / administration of blood product (other than suspect drug):	Yes ☐	No ☐
Transplant:	Yes ☐	No ☐
Childbirth:	Yes ☐	No ☐

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Safety & Pharmacovigilance * 655 Elizabeth Street * Melbourne , Victoria Australia 3000 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Questionnaire on Transmission of Infectious Agents

7. Medical History and Risk Factors

Surgery:	Yes ☐	No ☐
Visit to Dentist in the last 12 months:	Yes ☐	No ☐
Visit to Tattooists in the last 12 months:	Yes ☐	No ☐
Body piercing in the last 12months:	Yes ☐	No ☐
Acupuncture in the last 12 months:	Yes ☐	No ☐
Sexual practice (unprotected intercourse) in the last 12 months:	Yes ☐	No ☐
Other (specify):	Yes ☐	No ☐

8. Concomitant Medications?

Yes ☐ If yes, specify below No ☐ Unknown ☐

Drug	Dose	Route	Indication for Use	Start date	Stop date

9. Details of Laboratory Testing

Test performed	Value prior to administration	Date (dd/mmm/yyyy)	Value post-administration	Date (dd/mmm/yyyy)
Anti-HAV IgG				
Anti-HAV IgM				
HBsAg				
Anti-HBs IgG				
Anti-HBs IgM				
HBcAg				
Anti-HBc IgG				
Anti-HBc IgM				
HBeAg				
Anti-HBe IgG				
Anti-HBe IgM				
Anti-HCV				
HCV RNA				
Anti-HIV IgG				
Anti-HIV IgM				
Anti-B19 IgG				
Anti-B19 IgM				
Other infectious agents: specify:				

For laboratory values, indicate: : positive = + negative = - Not determined = ND (titre entries if applicable)

CSL Behring Innovation GmbH * Global Safety & Pharmacovigilance * P.O. Box 12 30 * 35002 Marburg, Germany * Fax +49-6421-39-4775 *
CSL Behring LLC * Global Safety & Pharmacovigilance * 1020 First Avenue, * King of Prussia, PA, 19406-0901, U.S.A. * Fax +1-610-878-4487 *
CSL * Global Safety & Pharmacovigilance * 655 Elizabeth Street * Melbourne , Victoria Australia 3000 * Fax +61-3-9389-1095 *
Email: Adverse.Events.Global@cslbehring.com

Questionnaire on Transmission of Infectious Agents

10. Details and results of any other relevant investigation/s

11. Current status and details on any planned follow up

12. Other relevant information

☐ **No Further Information Available**

13. Reporter Information

This form also requests some information about you, the reporter/treating health care professional. This information will be used by CSL in conjunction with any follow up investigation of the event by CSL. This information may also be accessed by other members of the CSL Group of companies and relevant licencing partners (some of which are resident overseas) as part of CSL's global adverse event reporting database. If this information is not provided it may adversely affect our investigation. All personal data in this report will be kept protected and confidential in line with our Company Privacy Policy and data protection legislation (see Global Privacy Policy | CSL for Privacy Notice). The information provided will solely be used for pharmacovigilance obligations and may be reported in anonymized form to health authorities, where required by law. You have a right to access your personal data which we hold about you by contacting our Privacy Officer via email notification to privacy@cslbehring.com

Details of Reporter **Is this a consumer / patient report?** ☐ Yes ☐ No (If yes, has the patient given consent to CSL to follow up the adverse reaction report with the healthcare professional?) ☐ Yes ☐ No If consent to follow up with healthcare professional was not given, does the patient give consent to CSL to be contacted regarding this adverse event report? ☐ Yes ☐ No	**Details of Treating Health Care Professional** (If different from Reporter)
Occupation:	Occupation:
Full Name:	Full Name:
Organisation/Address:	Organisation/Address:
Telephone: Fax	Telephone: Fax
Email:	Email:

Document Approvals

Approved Date: 13 Nov 2024

Task: Approval Task Verdict: Approve	PPD 04-Nov-2024 09:16:35 GMT+0000
Task: Approval Task Verdict: Approve	PPD 13-Nov-2024 01:39:41 GMT+0000
Task: QA Approval Verdict: Approve	PPD 13-Nov-2024 09:07:59 GMT+0000

Annex 6 Details of proposed additional risk minimisation activities (if applicable)

Not applicable

Annex 7 Other supporting data (including referenced material)

REFERENCES

Alotaibi GS, Wu C, Senthilselvan A, McMurtry MS. Secular trends in incidence and mortality of acute venous thromboembolism: The AB-VTE Population-Based Study. Am J Med. 2016;129(8), 879:e819-25.

Alshekhlee A, Hussain Z, Sultan B, Katirji B. Guillain-Barré syndrome: incidence and mortality rates in US hospitals. Neurology. 2008;70(18):1608-13.

American Academy of Allergy, Asthma and Immunology (AAAAI). The Allergy Report: Science Based Findings on the Diagnosis & Treatment of Allergic Disorders. 1996-2010.

Arason GJ, Jorgensen GH, Ludviksson BR. Primary immunodeficiency and autoimmunity: lessons from human diseases. Scand J Immunol. 2010;71(5):317-28.

Arshad N, Isaksen T, Hansen JB, Braekkan SK. Time trends in incidence rates of venous thromboembolism in a large cohort recruited from the general population. Eur J Epidemiol. 2017;32(4):299-305.

Asia Pacific Immunoglobulins in Immunology Expert Group I (APIIEG). Consensus Recommendations for the use of Immunoglobulin Replacement Therapy in Immune Deficiency. 2009.

Badros A, Barlogie B, Siegel E, Morris C, Desikan R, Zangari M, et al. Autologous stem cell transplantation in elderly multiple myeloma patients over the age of 70 years. Br J Haematol. 2001;114(3):600-7.

Bamberger DM. Diagnosis, initial management, and prevention of meningitis. Am Fam Physician. 2010;82(12):1491-8.

Bellac CL, Hottiger T, Jutzi MP, Bogli-Stuber K, Sanger M, Hanschmann KM, et al. The role of isoagglutinins in intravenous immunoglobulin-related hemolysis. Transfusion. 2015;55(Suppl 2):S13-22.

Berg R, Fuellenhals E. Aseptic meningitis following therapy with immune globulins: a combination of product features and patient characteristics? Transfusion. 2016;56(12):3021-8.

Biggar RJ, Taha TE, Hoover DR, Yellin F, Kumwenda N, Broadhead R. Higher in utero and perinatal HIV infection risk in girls than boys. J Acquir Immune Defic Syndr. 2006;41(4):509-13.

Bouchard C, Lacroix C, Planté V, Adams D, Chedru F, Guglielmi JM, et al. Clinicopathologic findings and prognosis of chronic inflammatory demyelinating polyneuropathy. Neurology. 1999;52(3):498-503.

Bousfiha AA, Jeddane L, Ailal F, Benhsaien I, Mahlaoui N, Casanova J-L, et al. Primary immunodeficiency diseases worldwide: more common than generally thought. J Clin Immunol. 2013;33(1):1-7.

Boyle JM, Buckley RH. Population prevalence of diagnosed primary immunodeficiency diseases in the United States. J Clin Immunol. 2007;27(5):497-502.

Bresee JS, Mast EE, Coleman PJ, Baron MJ, Schonberger LB, Alter MJ et al. Hepatitis C Virus infection associated with administration of intravenous immune globulin a cohort study. JAMA. 1996;276(19):1563-7.

Bright RJ, Wilkinson J, Coventry BJ. Therapeutic options for chronic inflammatory demyelinating polyradiculoneuropathy: a systematic review. BMC Neurol. 2014;14:26.

Brown HC, Ballas ZK. Acute thromboembolic events associated with intravenous immunoglobulin infusion in antibody-deficient patients. J Allergy Clin Immunol. 2003;112(4):797-9.

Buchanan AM, Dow DE, Massambu CG, Nyombi B, Shayo A, Musoke R, et al. Progress in the prevention of mother to child transmission of HIV in three regions of Tanzania: a retrospective analysis. PLoS One. 2014;9(2):e88679.

Cao-Lormeau VM, Blake A, Mons S, Lastere S, Roche C, Vanhomwegen J, et al. Guillain-Barré syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. The Lancet. 2016;387(10027):1531-9.

Caress JB, Kennedy BL, Eickman KD. Safety of intravenous immunoglobulin treatment. Expert Opin Drug Saf. 2010;9(6):971-9.

Castelli R, Gualtierotti R, Orofino N, Losurdo A, Gandolfi S, Cugno M. Current and emerging treatment options for patients with relapsed myeloma. Clin Med Insights Oncol. 2013;7:209-19.

Cats EA, van der Pol WL, Piepers S, Franssen H, Jacobs BC, van den Berg-Vos RM, et al. Correlates of outcome and response to IVIg in 88 patients with multifocal motor neuropathy. Neurology. 2010;75(9):818-25.

Center for Disease Control and Prevention. [Internet]. 2024. Measles symptoms and complications. Available from: https://www.cdc.gov/measles/signs-symptoms/

Cines DB, Blanchette VS. Immune thrombocytopenic purpura. N Engl J Med. 2002;346(13):995-1008.

Coebergh JW, Janssen-Heijnen ML, Post PN, Razenberg PP. Serious co-morbidity among unselected cancer patients newly diagnosed in the southeastern part of The Netherlands in 1993-1996. J Clin Epidemiol. 1999;52(12):1131-6.

Collins KP, Patterson TL. Transfusion-related acute lung injury: what the allied health professional needs to know about the life-threatening hazard of blood transfusion. IJAHSP. 2014;12(2).

Colovic M, Dimitrijevic M, Sonnenburg C, Suvajdzic N, Donfrid M, Bogdanovic A. Clinical efficacy and safety of a novel intravenous immunoglobulin preparation in adult chronic ITP. Hematol J. 2003;4(5):358-62.

Cooper MD, Lanier LL, Conley ME, Puck JM. Immunodeficiency disorders. Hematology Am Soc Hematol Educ Program. 2003:314-30.

Copelan EA, Strohm PL, Kennedy MS, Tutschka PJ. Hemolysis following intravenous immune globulin therapy. Transfusion. 1986;26(5):410-2.

Dalakas MC. High-dose intravenous immunoglobulin and serum viscosity: risk of precipitating thromboembolic events. Neurology. 1994;44(2):223-6.

Dalakas MC, Clark WM. Strokes, thromboembolic events, and IVIg: rare incidents blemish an excellent safety record. Neurology. 2003;60(11):1736-7.

Dantal J. Intravenous immunoglobulins: in-depth review of excipients and acute kidney injury risk. Am J Nephrol. 2013;38(4):275-84.

Daw Z, Padmore R, Neurath D, Cober N, Tokessy M, Desjardins D, et al. Hemolytic transfusion reactions after administration of intravenous immune (gamma) globulin: a case series analysis. Transfusion. 2008;48(8):1598-601.

Debes A, Bauer M, Kremer S. Tolerability and safety of the intravenous immunoglobulin Octagam: a 10-year prospective observational study. Pharmacoepidemiol Drug Saf. 2007;16(9):1038-47.

Deenen JC, Horlings CG, Verschuuren JJ, Verbeek AL, van Engelen BG. The epidemiology of neuromuscular disorders: a comprehensive overview of the literature. J Neuromuscul Dis. 2015;2(1):73-85.

Dickenmann M, Oettl T, Mihatsch MJ. Osmotic nephrosis: acute kidney injury with accumulation of proximal tubular lysosomes due to administration of exogenous solutes. Am J Kidney Dis. 2008;51(3):491-503.

D'Souza A, Fretham C. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR summary slides. 2017. Available from: http://www.cibmtr.org

European Centre for Disease Prevention and Control (ECDC); 2023. Measles Annual Epidemiological Report for Measles 2023. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/MEAS_AER_2023_Report.pdf and Factsheets about Measles. Available from: https://www.ecdc.europa.eu/en/measles/facts

Erdmann PG, Lindeman E, Cats EA, van den Berg LH. Functioning of patients with multifocal motor neuropathy. J Peripher Nerv Syst. 2010;15(2):113-9.

Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2017;3(4):524-48.

Fogarty PF, Segal JB. The epidemiology of immune thrombocytopenia purpura. Curr Opin Hematol. 2007;14(5):515-9.

Fowkes FJ, Price JF, Fowkes FG. Incidence of diagnosed deep vein thrombosis in the general population: systematic review. Eur J Vasc Endovasc Surg. 2003;25(1):1-5.

Frangoul H, Min E, Wang W, Chandrasekhar R, Calder C, Evans M, et al. Incidence and risk factors for hypogammaglobulinemia in pediatric patients following allo-SCT. Bone Marrow Transplant. 2013;48(11):1456-9.

Galeotti F, Massari M, D'Alessandro R, Beghi E, Chiò A, Logroscino G, et al. Risk of Guillain-Barré syndrome after 2010-2011 influenza vaccination. Eur J Epidemiol. 2013;28(5):433-44.

Gardulf A. Immunoglobulin treatment for primary antibody deficiencies: advantages of the subcutaneous route. BioDrugs. 2007;21(2):105-16.

GBD; 2017 Collaborators. Available from: http://ghdx.healthdata.org/gbd-results-tool

Ghia P, Ferreri AJM, Caligaris-Cappio F. Chronic lymphocytic leukemia. Crit Rev Oncol Hematol. 2007;64:234-46.

Golding B. Immune globulin intravenous (Human) (IGIV); Required updates to Product Labelling. 2003 Oct 16. Available from: http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm093491.htm)

Gordon DJ, Sloan SR, de Jong JL. A pediatric case series of acute hemolysis after administration of intravenous immunoglobulin. Am J Hematol. 2009;84(11):771-2.

Govoni V, Granieri E. Epidemiology of the Guillain-Barré syndrome. Curr Opin Neurol. 2001;14(5):605-13.

Hafsteinsdottir B, Olafsson E. Incidence and natural history of idiopathic chronic inflammatory demyelinating polyneuropathy: a population-based study in Iceland. Eur Neurol. 2016;75(5-6):263-8.

Hamblin AD, Hamblin TJ. The immunodeficiency of chronic lymphocytic leukaemia. Br Med Bull. 2008;87:49-62.

Hamblin TJ. Chronic lymphocytic leukaemia. Bailliere Clin Haematol. 1987;1:449-91.

Hamrock DJ. Adverse events associated with intravenous immunoglobulin therapy. Int Immunopharmacol. 2006;6(4):535-42.

Holman RC, Belay ED, Christensen KY, Folkema AM, Steiner CA, Schonberger LB. Hospitalizations for Kawasaki syndrome among children in the United States, 1997-2007. Pediatr Infect Dis J. 2010;29(6):483-8.

Hopkins S, Jolles S. Drug-induced aseptic meningitis. Expert Opin Drug Saf. 2005;4(2):285-97.

Horn J, Thon V, Bartonkova D, Salzer U, Warnatz K, Schlesier M. Anti-IgA antibodies in common variable immunodeficiency (CVID): diagnostic workup and therapeutic strategy. Clin Immunol. 2007;122(2):156-62.

Hughes RA, Rees JH. Clinical and epidemiologic features of Guillain-Barre syndrome. J Infect Dis. 1997;176:92-8.

Institute for Health Metrics and Evaluation (IHME). 2019. GBD Results Tool. Available from: http://ghdx.healthdata.org/gbd-results-tool

Irani DN. Aseptic meningitis and viral myelitis. Neurol Clin. 2008;26(3):635-55.

Isma N, Svensson PJ, Gottsäter A, Lindblad B. Prospective analysis of risk factors and distribution of venous thromboembolism in the population-based Malmö Thrombophilia Study (MATS). Thromb Res. 2009;124(6):663-6.

Jamieson N, Singh-Grewal D. Kawasaki disease: a Clinician's Update. Int J Pediatr. 2013;2013:645391.

Joshi AV, Iyer VN, Hagan JB, St Sauver JL, Boyce TG. Incidence and temporal trends of primary immunodeficiency: a population-based cohort study. Mayo Clin Proc. 2009;84(1):16-22.

Kahwaji J, Barker E, Pepkowitz S, Klapper E, Villicana R, Peng A, et al. Acute hemolysis after high-dose intravenous immunoglobulin therapy in highly HLA sensitized patients. Clin J Am Soc Nephrol. 2009;4(12):1993-7.

Kashiwagi H, Tomiyama Y. Pathophysiology and management of primary immune thrombocytopenia. Int J Hematol. 2013;98(1):24-33.

Katagiri D, Noiri E, Hinoshita F. Multiple myeloma and kidney disease. Sci World J. 2013;2013:487285.

Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. Arerugi. 1967;16:178-222 (in Japanese).

Khan F, Pallant JF, Ng L, Bhasker A. Factors associated with long-term functional outcomes and psychological sequelae in Guillain-Barre syndrome. J Neurol. 2010;257(12):2024-31.

Kobrynski L, Powell RW, Bowen S. Prevalence and morbidity of primary immunodeficiency diseases, United States 2001-2007. J Clin Immunol. 2014;34(8):954-61.

Komenda M, Stadler D, Malinas T, Moses M, Pragst I, Herzog E, et al. Assessment of the ability of the Privigen(R) purification process to deplete thrombogenic factor XIa from plasma. Vox Sang. 2014;107:26-36.

Krauer F, Riesen M, Reveiz L, Oladapo OT, Martínez-Vega R, Porgo TV, et al. Zika virus infection as a cause of congenital brain abnormalities and Guillain–Barré syndrome: systematic review. PLOS Med. 2017;14(1):e1002203.

Kristinsson SY, Landgren O, Dickman PW, Derolf AR, Björkholm M. Patterns of survival in multiple myeloma: a population-based study of patients diagnosed in Sweden from 1973 to 2003. J Clin Oncol. 2007; 25(15):1993-9.

Ku F, Tsai CR, Der Wang J, Wang CH, Chang TK, Hwang WL. Stromal-derived factor-1 gene variations in pediatric patients with primary immune thrombocytopenia. Eur J Haematol. 2013;90(1):25-30.

Kumar R. Aseptic meningitis: diagnosis and management. Indian J Pediatr. 2005;72(1):57-63.

Kuwabara S. Guillain-Barré syndrome: epidemiology, pathophysiology and management. Drugs. 2004;64(6):597-610.

Lawson VH, Arnold WD. Multifocal motor neuropathy: a review of pathogenesis, diagnosis, and treatment. Neuropsychiatr Dis Treat. 2014;10:567-76.

Laughlin RS. Incidence and prevalence of CIDP and the association of diabetes mellitus. Neurology. 2009;73(1):39-45.

Lee BE, Davies HD. Aseptic meningitis. Curr Opin Infect Dis. 2007;20(3):272-7.

Lenz HJ. Management and preparedness for infusion and hypersensitivity reactions. Oncologist. 2007;12(5):601-9.

Lin RY, Rodriguez-Baez G, Bhargave GA, Lin H. Intravenous gammaglobulin-associated renal impairment reported to the FDA: 2004 - 2009. Clin Nephrol. 2011;76(5):365-72.

Löscher WN, Oberreiter EM, Erdler M, Quasthoff S, Culea V, Berek K, et al. Multifocal motor neuropathy in Austria: a nationwide survey of clinical features and response to treatment. J Neurol. 2018;265(12):2834-40.

Mahdi-Rogers M, Hughes RAC. Epidemiology of chronic inflammatory neuropathies in southeast England. Eur J Neurol. 2014;21(1):28-33.

Makino N, Nakamura Y, Yashiro M, Sano T, Ae R, Kosami K, et al. Epidemiological observations of Kawasaki disease in Japan, 2013-2014. Pediatr Int. 2018;60(6):581-7.

Marr KA. Delayed opportunistic infections in hematopoietic stem cell transplantation patients: a surmountable challenge. Hematology Am Soc Hematol Educ Program. 2012;2012:265-70.

Martinez C, Watson DJ, Shebl A, Wallenhorst C, Hubsch A, Simon TL. Impact of screening and exclusion of high anti-A titer donors on the risk of hemolytic anemia with intravenous immunoglobulin treatment: a hospital-based cohort study in the US. Am J Hematol. 2018;93(1):E17-20.

Martino A, Campa D, Jurczyszyn A, Martínez-López J, Moreno MJ, Varkonyi J, et al. Genetic variants and multiple myeloma risk: IMMEnSE validation of the best reported associations—an extensive replication of the associations from the candidate gene era. Cancer Epidemiol Biomarkers Prev. 2014;23(4):670-4.

McLeod JG, Pollard JD, Macaskill P, Mohamed A, Spring P, Khurana V. Prevalence of chronic inflammatory demyelinating polyneuropathy in New South Wales, Australia. Ann Neurol. 1999;46(6):910-3.

Michel M. Immune thrombocytopenic purpura: epidemiology and implications for patients. Eur J Haematol Suppl. 2009;(71):3-7.

Mielke O, Fontana S, Goranova-Marinova V, Shebl A, Spycher MO, Wymann S, et al. Hemolysis related to intravenous immunoglobulins is dependent on the presence of

anti-blood group A and B antibodies and individual susceptibility. Transfusion. 2017;57(11):2629-38.

Minta AA, Ferrari M, Antoni S, Lambert B, Sayi TS, Hsu CH, et al. Progress toward measles elimination — worldwide, 2000–2023. MMWR Morb Mortal Wkly Rep. 2024;73:1036-42.

Mirakian R, Ewan PW, Durham SR, Youlten LJ, Dugué P, Friedmann PS, et al. BSACI guidelines for the management of drug allergy. Clin Exp Allergy. 2009;39(1):43-61.

Misbah SA, Chapel HM. Adverse effects of intravenous immunoglobulin. Drug Saf. 1993;9(4):254-62.

Moro Moro M, Tejedor Alonso MA, Esteban Hernández J, Múgica García MV, Rosado Ingelmo A, Vila Albelda C. Incidence of anaphylaxis and subtypes of anaphylaxis in a general hospital emergency department. J Investig Allergol Clin Immunol. 2011;21(2):142-9.

Morrison VA. Infectious complications of chronic lymphocytic leukaemia: pathogenesis, spectrum of infection, preventive approaches. Best Pract Res Clin Haematol. 2010;23:145-53.

Moulis G, Sailler L, Sommet A, Lapeyre-Mestre M, Montastruc J. Description of intravenous immune-globulins-induced renal failure in the French Pharmacovigilance database. Fundam Clin Pharmacol. 2011;25:99.

Nachamkin I, Allos BM, Ho T. Campylobacter species and Guillain-Barré syndrome. Clin Microbiol Rev. 1998;11(3):555-67.

Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Circulation. 2004;110(17):2747-71.

Notarangelo L, Casanova J-L, Fischer A, Puck J, Rosen F, Seger R, et al. Primary immunodeficiency diseases: an update. J Allergy Clin Immunol. 2004;114:677-87.

National Vaccine Information Center (NVIC). Risk factor for measles. Available from: https://www.nvic.org/disease-vaccine/measles/highest-risk

Onouchi Y, Gunji T, Burns JC, Shimizu C, Newburger JW, Yashiro M, et al. ITPKC functional polymorphism associated with Kawasaki disease susceptibility and formation of coronary artery aneurysms. Nature Genetics. 2008;40(1):35-42.

Onuigbo MA. Exposure to inhibitors of the renin-angiotensin system is a major independent risk factor for acute renal failure induced by sucrose containing intravenous immunoglobulins. A case-control study. Pharmacoepidemiol Drug Saf. 2012;21(3):320-2.

Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. Allergy Clin Immunol. 2006;117(4 Suppl):S525-53.

Oscier D, Dearden C, Eren E, Fegan C, Follows G, Hillmen P, et al. Guidelines on the diagnosis, investigation and management of chronic lymphocytic leukaemia. Br J Haematol. 2012;159:541-64.

Palumbo A, Cerrato C. Diagnosis and therapy of multiple myeloma. Korean J Intern Med. 2013;28(3):263-73.

Paran D, Herishanu Y, Elkayam O, Shopin L, Ben-Ami R. Venous and arterial thrombosis following administration of intravenous immunoglobulins. Blood Coagul Fibrinolysis. 2005;16(5):313-8.

Passweg JR, Baldomero H, Bader P, Basak GW, Bonini C, Duarte R, et al. European Society for Blood and Marrow Transplantation (EBMT). Is the use of unrelated donor transplantation leveling off in Europe? The 2016 European Society for Blood and Marrow Transplant Activity Survey Report. Bone Marrow Transplant. 2018;53(9):1139-48.

Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. Transfus Med Rev. 2003;17(4):241-51.

Pinna GS, Kafetzis DA, Tselkas OI, Skevaki CL. Kawasaki disease: an overview. Curr Opin Infect Dis. 2008;21(3):263-70.

Piot P, Quinn TC. Response to the AIDS pandemic – a global health model. N Engl J Med. 2013;368(23):2210-8.

Quinti I, Soresina A, Agostini C, Spadaro G, Matucci A, Sfika I, et al. Prospective study on CVID patients with adverse reactions to intravenous or subcutaneous IgG administration. J Clin Immunol. 2008;28(3):263-7.

Radder CM, Roelen DL, Van de Meer-Prins EM, Claas FHJ, Kanhai HHH, Brand A. The immunologic profile of infants born after maternal immunoglobulin treatment and intrauterine platelet transfusions for fetal/neonatal alloimmune thrombocytopenia. Am J Obstet Gynecol. 2004;191:815-20.

Razvi S, Schneider L, Jonas MM, Cunningham-Rundles C. Outcome of intravenous immunoglobulin-transmitted hepatitis C virus infection in primary immunodeficiency. Clin Immunol. 2001;101(3):284-8.

Reisman M, Caspi A. Immune globulin subcutaneous (human): vivaglobin P&T Product Profiler. 2009;34(6) Section 2:1-26.

Ripellino P, Fleetwood T, Cantello R, Comi C. Treatment of chronic inflammatory demyelinating polyneuropathy: from molecular bases to practical considerations. Autoimmune Dis. 2014;2014:201657.

Roger VL, Weston SA, Gerber Y, Killian JM, Dunlay SM, Jaffe AS, et al. Trends in incidence, severity, and outcome of hospitalized myocardial infarction. Circulation. 2010;121(7):863-9. doi:10.1161/CIRCULATIONAHA.109.897249

Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet. 1999;353(9159):1167-73.

Rozman C, Montserrat E. Chronic lymphocytic leukemia. N Engl J Med. 1995;333(16):1052-7.

Rubin Z, Pappalardo A, Schwartz A, Antoon JW. Prevalence and outcomes of primary immunodeficiency in hospitalized children in the United States. J Allergy Clin Immunol Pract. 2018;6(5):1705-10.e1701

Rudolph T, Larsen JP, Farbu E. The long-term functional status in patients with Guillain-Barré syndrome. Eur J Neurol. 2008;15(12):1332-7.

Saba HI, Hartmann RC, Herion JC. Hemophilus influenzae septicemia and polyarthritis in multiple myeloma. South Med J. 1979;72:743-6.

Sandler SG, Eder AF, Goldman M, Winters JL. The entity of immunoglobulin A-related anaphylactic transfusion reactions is not evidence based. Transfusion (Paris) 2015;55:199-204.

Sarpatwari A, Bennett D, Logie JW, Shukla A, Beach KJ, Newland AC, et al. Thromboembolic events among adult patients with primary immune thrombocytopenia in the United Kingdom General Practice Research Database. Haematologica. 2010;95(7):1167-75.

Schiavotto C, Ruggeri M, Rodeghiero F. Adverse reactions after high-dose intravenous immunoglobulin: incidence in 83 patients treated for idiopathic thrombocytopenic purpura (ITP) and review of the literature. Haematologica. 1993;78(6 Suppl 2):35-40.

Scribner C, Kapit R, Phillips E, Rickels N. Aseptic meningitis and intravenous immunoglobulin therapy. Ann Intern Med. 1994;121:305-6.

Schnyder B, Pichler WJ. Mechanisms of drug-induced allergy. Mayo Clin Proc. 2009;84(3):268-72.

Sehgal S, Chen X, Ang JY. Epidemiology, clinical presentation, and outcomes of kawasaki disease among hospitalized children in an inner city hospital before and after publication of the American Academy of Pediatrics/American Heart Association Guidelines for Treatment of Kawasaki Disease: An 11-Year Period. Clin Pediatr (Phila). 2015;54(13):1283-9.

Sejvar JJ, Baughman AL, Wise M, Morgan OW. Population incidence of Guillain-Barré syndrome: a systematic review and meta-analysis. Neuroepidemiology. 2011;36(2):123-33.

Sekul EA, Cupler EJ, Dalakas MC. Aseptic meningitis associated with high-dose intravenous immunoglobulin therapy: frequency and risk factors. Ann Intern Med. 1994;121(4):259-62.

Sewell WAC, Kerr J, Behr-Gross M-E, Peter H-H, on behalf of the Kreuth Ig Working G. European consensus proposal for immunoglobulin therapies. Eur J Neurol. 2014;44(8):2207-14.

Shebl A, Gabriel S, Hubsch A, Hoefferer L, Welsh S. Isoagglutinin reduction in IVIG by specific immunoaffinity chromatography reduces spontaneous reporting rates of hemolytic reactions. J Peripher Nerv Syst. 2018;23(4):270.

Shebl A, Gabriel S, Van Dinther K, Hubsch A, Hoefferer L, Welsh S. Reduction in spontaneous reporting rates of hemolysis with IVIG after implementation of an

immunoaffinity chromatography step for isoagglutinin reduction. J Allergy Clin Immunol. 2019;143(2 Suppl).

Shebl A, Mallick A, Fescharek F, Patel G, Hoefferer L, Gabriel S, et al. Reduction of isoagglutinins in intravenous immunoglobulin by anti-A donor screening and spontaneous reporting rates of haemolytic reactions worldwide. J Peripher Nerv Syst. 2016;21(3):210.

Shemer A, Kivity S, Shoenfeld Y. Clinical indications for intravenous immunoglobulin utilization in a tertiary medical center: a 9-year retrospective study. Transfusion. 2018;58(2):430-8.

Silliman CC, Ambruso DR, Boshkov LK. Transfusion-related acute lung injury. Blood. 2005;105(6):2266-73.

Simons FE, Ardusso LR, Dimov V, Ebisawa M, El-Gamal YM, Lockey RF, et al. World Allergy Organization Anaphylaxis Guidelines: 2013 update of the evidence base. Int Arch Allergy Immunol. 2013;162(3):193-204.

Singer P, Cohen J, Cynober L. Effect of nutritional state of brain-dead organ donor on transplantation. Nutrition. 2001;17(11-12):948-52.

Singh S, Vignesh P, Burgner D. The epidemiology of Kawasaki disease: a global update. Arch Dis Child 2015;100:1084-8.

Soilleux EJ, Coleman N. Transplacental transmission of HIV: a potential role for HIV binding lectins. Int J Biochem Cell Biol. 2003;35(3):283-7.

Spycher M, Bolli R, Hodler G, Gennari K, Hubsch A, Späth P. Well-tolerated liquid intravenous immunoglobulin G preparations (IVIG) have a low immunoglobulin G dimer (IgG-dimer) content. J Autoimmun. 1999;96(Suppl 1):96.

Sridhar G, Ekezue BF, Izurieta HS, Forshee RA, Selvam N, Mintz PD, et al. Occurrence of hemolytic reactions on the same day as immune globulin product administrations during 2008 to 2014. Transfusion. 2018;58(1):70-80.

Stangel M, Kiefer R, Pette M, Smolka MN, Marx P, Gold R. Side effects of intravenous immunoglobulins in neurological autoimmune disorders--a prospective study. J Neurol. 2003;250(7):818-21.

Taylor E. Intravenous immune globulin (IVIG): hemolytic reactions. CARN. 2009;14(4):1-3.

Thamavit W, Pairojkul C, Tiwawech D, Shirai T, Ito N. Lack of promoting effect of proline on bile duct cancer development in dimethylnitrosamine-initiated hamster livers. Teratog Carcinog Mutagen. 1994;14:169-74.

Thomas MJ, Misbah SA, Chapel HM, Jones M, Elrington G, Newsom-Davis J. Hemolysis after high-dose intravenous Ig. Blood. 1993;82(12):3789.

Thorsteinsdottir S, Dickman PW, Landgren O, Blimark C, Hultcrantz M, Turesson I, et al. Dramatically improved survival in multiple myeloma patients in the recent decade: results from a Swedish population-based study. Haematologica. 2018;103(9):e412-5.

Victoriano AF, Imai K, Okamoto T. Interaction between endogenous bacterial flora and latent HIV infection. Clin Vaccine Immunol. 2013;20(6):773-9.

Vlaar APJ, Juffermans NP. Transfusion-related acute lung injury: a clinical review. The Lancet. 2013;382(9896):984-94.

Vos T, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study. The Lancet. 2016;2016; 390(10100):1211-59.

Warrington R, Silviu-Dan F. Drug allergy. Allergy Asthma Clin Immunol. 2011;7(Suppl 1):S10.

WHO; 2017. Available from: http://www.who.int/hiv/data/2017_summary-global-hiv-epidemic.png?ua=1

WHO; 2025. Measles. Available from: https://www.who.int/news-room/fact-sheets/detail/measles

Widimsky P, Wijns W, Fajadet J, de Belder M, Knot J, Aaberge L. European association for percutaneous cardiovascular interventions. reperfusion therapy for ST elevation acute myocardial infarction in Europe: description of the current situation in 30 countries. Eur Heart J. 2010;31(8):943-57.

Winer JB. An update in guillain-barré syndrome. Autoimmune Diseases. 2014;2014:793024.

Wolff AE, Hansen KE, Zakowski L. Acute Kawasaki disease: not just for kids. J Gen Intern Med. 2007;22(5):681-4.

World Allergy Organization. White Book on Allergy 2011-2012.

Signature Page

IgPro10, IVIG (10% Human) - Risk Management Plan - RMP_v9.1_DLP_31-Dec-2025_redacted version

Signed By	Date (GMT)
Bonagua, Ellen	05-May-2026 13:53:15
Approved-EU-QPPV (or delegate) Approval	

--- Do Not Detach This Signature Page ---